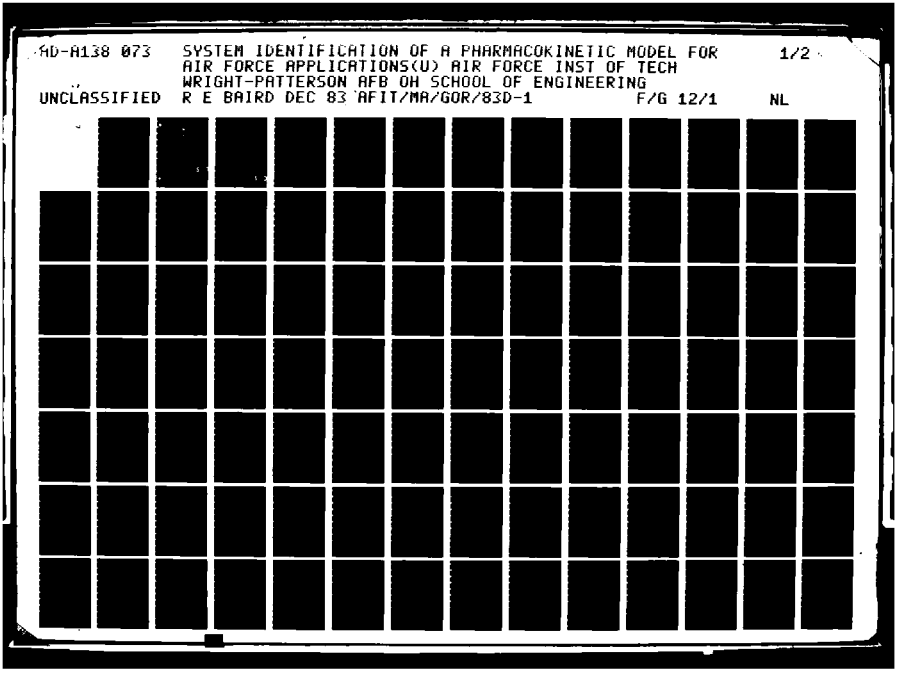
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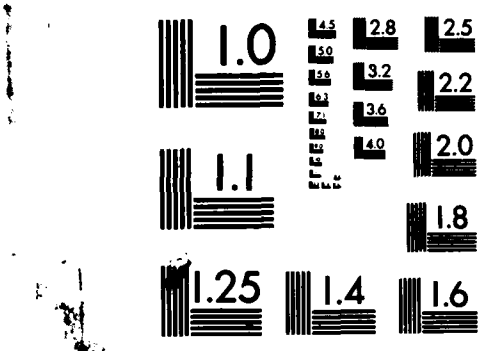

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SYSTEM IDENTIFICATION OF A PHARMACOKINETIC MODEL FOR AIR FORCE APPLICATIONS

THESIS

Ronald E. Baird
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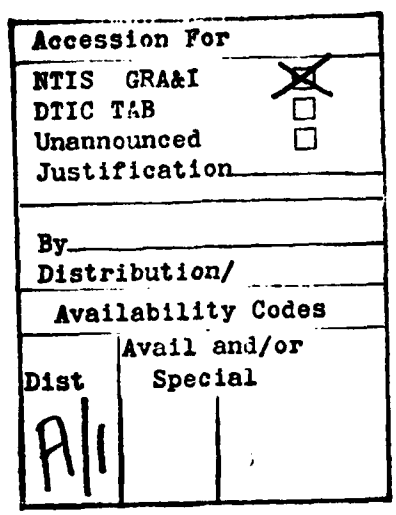

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THESIS

Presented to the Faculty of the School of Engineering

of the Air Force Institute of Technology

Air University

In Partial Fulfillment of the

Requirements for the Degree of

Master of Science in Operations Research

Ronald E. Baird, B.S.

First Lieutenant, USAF

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Table of Contents

the Air Force Aerospace Medical Research Laboratory (AFAMRL).

Abstract

Methods for enhancing the parameter estimation process of pharmacokinetic models were examined and implemented for AFAMRL. The Open Chamber Hexane Model was the primary focus. Optimization algorithms were developed and used to estimate the unknown parameters in order that the model match closely with the experimental data. A sensitivity analysis was then conducted in two parts. First, the sensitivity of the estimated parameters to the error criterion was examined. Second, the use of sensitivity functions in designing future experiments was demonstrated. Finally, recommendations were provided for AFAMRL concerning future attempts in parameter estimation.

I. INTRODUCTION

At the Air Force Aerospace Medical Research Laboratory (AFAMRL), researchers are studying the effects of toxic substances on mammals. One reason is that Air Force personnel are occasionally exposed to toxic substances. By understanding how these substances affect man, the researchers can aid Air Force decision makers in choosing those materials safest for Air Force use.

In their work, the researchers generally follow three steps. First, they develop a mathematical model that represents the chemical processes in the mammal. This model is referred to as a pharmacokinetic model. Next, the researchers design experiments to collect data. Finally, they estimate any unknown parameters in the model by selecting the ones that provide the closest agreement between the model and the data. With the estimates of the parameters, the model is completely specified. This model is then used to predict the concentration level of toxic substances throughout the body.

The process of developing the pharmacokinetic model and designing the experiment has been successfully done at several

places, including Wright Patterson AFB. However, the process of choosing the estimates requires limited resources to solve the model and compare these solutions with the experimental data. Thus, parameter estimation is generally confined to facilities that can provide adequate support for solving pharmacokinetic models.

Before May of 1982, AFAMRL scientists conducted st of their pharmacokinetic calculations at the facilitie f Dow Chemical Company. The facilities were beneficial to research, but it failed to meet some of the scientists' needs. In addition, the facilities' location away from Wright Patterson AFB proved to be an inconvenience to the scientists. For these reasons, two scientists, Dr. Anderson and Major Clewell looked to the Mathematics Department at AFIT to help develop local support for their work.

In May of 1982, Mayberry (GCS-82D) initiated a thesis effort that successfully provided solutions of some pharmacokinetic models. This effort was the first step towards in-house estimation of the model parameters at Wright Patterson AFB. With Mayberry's computer programs, the researchers could try values for the unknown parameters and plot the model's results. By comparing these results with the actual data, the researchers would then adjust the values to make the model agree more closely with the data. This trial and error process of adjusting the values continued

until the model matched closely with the data.

Unfortunately, this process of parameter estimation is very tedious and time consuming. In the past, researchers have typically taken about one month to estimate the parameters. Yet, from their work they often discover changes necessary to the model. Then they once again must estimate the new model's parameters. In essence, the parameter estimation process is almost never ending. Because of this tedium, the researchers requested that a computer be used to free up their time and provide results much more quickly.

In addition to the tedium of parameter estimation, another problem encouraged the researchers to use the computer for parameter estimation. Some pharmacokinetic models have grown in complexity, in the number of unknown parameters, and in the number of measurements. As a result, it has become nearly impossible for the researchers to vary several parameters manually in order to fit the model to several data curves. For these models, computer support is almost necessary to estimate the parameters.

Problem Statement

Methods must be developed that improve the parameter estimation process of a pharmacokinetic model. In general, this includes any effort that helps speed the estimation process and guides the design of experiments. However, AFAMRL requires that these methods

be used to estimate the parameters of a model currently of interest.

Scope

This thesis effort only deals with the "Open Chamber Hexane Model". However, the principles involved will be general enough to apply to most of the models in which AFAMRL is interested. The computer programs developed are mainly intended to estimate the parameters of the Open Chamber Hexane Model. However, with minor modifications, they may be used to solve a large number of related models.

Assumptions

It is important to note that the model developed by AFAMRL is new. As a result, this thesis effort has run parallel with AFAMRL's continual updating of the model. With an eye focused towards supporting their research, the author has kept close contact with Dr. Anderson and Major Clewell. Any changes made by them have been incorporated in this thesis effort when possible. It is assumed, however, that the model reported in this thesis is the most correct form known.

General Approach

The first step in estimating the parameters of the Open

Chamber Hexane Model was to get the model and the experimental data. With the model and data, much of the literature was reviewed in order to locate topics that might aid in solving the problem. With a weighted least squares criterion for parameter estimation, optimization routines were developed for estimating the parameters. The optimization routines were then extensively used in a process of seeking the global minimum. Finally, a sensitivity analysis was conducted to evaluate the estimates and to provide clues about designing future experiments.

Sequence of Presentation

Chapter II first introduces the compartments associated with the Hexane Model. The differential equations are then derived for the model. The unknown parameters are specified next. Finally, the experimental data is obtained for the purpose of estimating the unknown parameters.

Chapter III reviews the literature in an attempt to gather together the background material relevant to parameter estimation. This chapter is meant to be a resource for this thesis effort as well as any future parameter estimation efforts.

Chapter IV derives the equations used for optimization with a weighted least squares error function. The Steepest Descent and the Scalar Gauss-Newton methods are the algorithms selected for

further use.

Chapter V uses the optimization routines to estimate the parameters. The final estimates and corresponding data plots were then reviewed by AFAMRL. The estimates were then accepted by AFAMRL for their applications.

Chapter VI looks at what happens to the error function when the final estimates are varied. This sensitivity analysis gives indications about the influence that the estimates have on the error function. Then, the sensitivity analysis is extended to cover some aspects that are relevant in the design of future experiments.

II. Formulation and Experimentation: The Open Chamber Hexane Model

This chapter specifies the items necessary before any attempt can be made to estimate parameters of a pharmacokinetic model. The first item is the equations of the pharmacokinetic model of interest. The model used in this thesis effort is the Open Chamber Hexane Model. The next items to be considered are the unknown parameters of the model. Finally, the experimental data used to estimate the unknown parameters is presented.

The Open Chamber Hexane Model

The chemical hexane is a substance contained in many materials and fuels widely used throughout the Air Force. As a result, the Air Force is interested in its effects on man. The Open Chamber Hexane Model was specifically formulated to describe these effects. Currently, the Hexane Model used by AFAMRL represents laboratory mammals rather than man. However, a few changes to the model's parameters are all that is needed for it to represent man. One problem with the model is that not all of its parameters are known. Estimating these parameters is

important in order to use the Hexane Model for Air Force applications.

To estimate some of these parameters, researchers first place laboratory mammals in test chambers. They then fill the chamber with hexane gas. At various instances in time, the gas concentration level is recorded. Simultaneously, researchers record the concentration levels in various parts of the mammal, such as the blood and body water. Together, these measurements provide the data set needed for parameter estimation.

For the experiment, researchers may choose to either control the gas concentration level throughout time or just set the initial gas concentration level. In the first case, the "Open Chamber" Model is used. The chamber is open in the sense that researchers maintain the desired input of hexane gas. The second case is known as the "Closed Chamber" Model. Once the experiment starts, no exchange of air is allowed between the chamber and its outside environment. Thus, the gas concentration level in the Closed Chamber Model is controlled only by the mammals' own metabolic processes and not by the experimenter.

Compartmental Model of the Open Chamber Hexane Model. To formulate pharmacokinetic models, researchers first represent the mammal as a set of compartments. Each compartment is typically an organ, tissue, or any part of the body where "the drug

concentration is assumed to be uniform." (MAYB82b: 2.6) Also, separate compartments are used to model different drugs that are found in the same area. Next, researchers connect these compartments to show where the chemicals are exchanged. A more detailed discussion on compartmental modelling is provided by Mayberry (MAY82b). In this section, the Open Chamber Hexane Model will be described with compartments.

When inhaled, the hexane gas basically undergoes two types of processes: (1) the distribution process and (2) the metabolic process. A distribution process is the transfer of the substance from one location in the body to another. The transfer does not change the chemical properties of the substance. For example, the transfer of the hexane gas from the lung to the blood is a distribution process. A metabolic process, on the other hand, is a process that changes the substance's chemical properties. New chemicals often result as by-products during the metabolism. These new substances are called metabolites. An example of metabolism is the oxidation of a substance by the liver. For the Hexane Model, the distribution process will be discussed first.

In the Hexane Model, five compartments are primarily involved in the distribution process. These compartments shown in Figure 2.1 are the Hexane in Lung, Hexane in Rapidly Perfused Tissue,

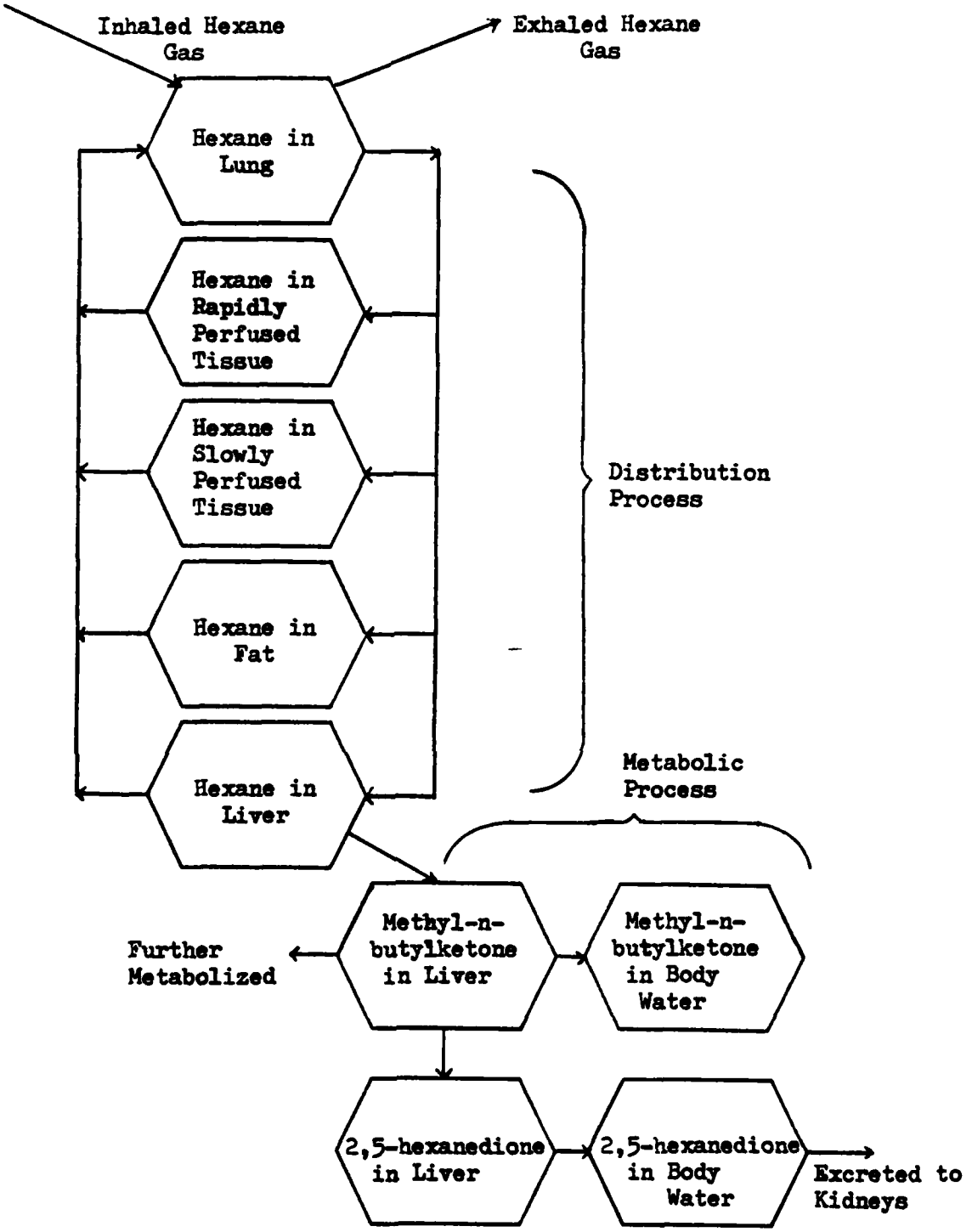

FIGURE 2.1 Compartmental model of the Open Chamber Hexane Model

Hexane in Slowly Perfused Tissue, Hexane in Fat, and Hexane in Liver. The distribution process begins when the mammal inhales the hexane gas into the lungs. From the lungs, hexane is transferred to the blood. The blood may be considered as a compartment, although this is not shown in Figure 2.1. The reason is that the gas enters and leaves the blood at a much higher rate than the other compartments. Thus, the concentration level in the blood is just a weighted combination of the concentration levels of each of the distribution compartments in its path. In essence, the blood performs the function of a transport medium. It distributes the hexane from the lung compartment to the other four compartments in the model.

The other four compartments in Figure 2.1 are involved with the metabolic processes. The metabolism begins when the hexane reaches the liver. Much of the hexane is oxidized into methyl-n-butylketone. The methyl-n-butylketone is then distributed to the body water, metabolized into 2,5-hexanedione, or metabolized into other substances that are currently not of interest. Subsequently, the 2,5-hexanedione in the liver is then distributed to the body water. Finally, the 2,5-hexanedione in the body water is then excreted to the kidneys.

Formulation of the Model Equations. With the compartmental model in Figure 2.1, the corresponding mathematical relationships are

derived. The equations involved are often referred to as mass balance equations. The formulation of the equations closely follows Mayberry's development, although Mayberry's formulation is primarily directed towards the chemical styrene (MAYB82b: CH 2). The parameters of the model are listed and defined in Table 2.1. Table 2.2 lists either the numerical values or the defining relationships used for the parameters. In addition, AFAMRL has indicated that the following relationships must be satisfied:

$$QC = QF + QL + QS + QR$$
$$CV = (QF*CVF + QL*CVL + QR*CVR + QS*CVS)/QC$$

The equations of the compartmental model will now be developed.

Lung Compartment. For the lung compartment, the mass balance equation is

$$dAI + (\text{amount entering from the venous blood}) = \qquad (2.1)$$
$$dAX + dAB + (\text{amount leaving with arterial blood})$$

This equation says that in a small time interval dt,

> the amount of hexane gas entering the lung compartment from inhaled air and venous blood returning from the body equals the amount of gas absorbed into the blood stream plus the amount of gas leaving the lung compartment in the arterial blood. (MAYB82b: 2.14)

TABLE 2.1 Parameters of the Open Chamber Hexane Model

AB = amount of hexane in capillary blood in the lungs (mg)
AF = amount of hexane in fat (mg)
AI = amount of hexane in inhaled air (mg)
AL1 = amount of hexane in liver (mg)
AL2 = amount of methyl-n-butylketone in liver (mg)
AL3 = amount of 2,5-hexanedione in liver (mg)
AM1 = amount of hexane metabolized into methyl-n-butylketone (mg)
AM2 = amount of methyl-n-butylketone metabolized into 2,5-hexanedione (mg)
AM3 = amount of methyl-n-butylketone metabolized into other metabolites
AR = amount of hexane in rapidly perfused tissue (mg)
AS = amount of hexane in slowly perfused tissue (mg)
AW1 = amount of methyl-n-butylketone in body water (mg)
AW2 = amount of 2,5-hexanedione in body water (mg)
AX = amount of hexane in exhaled air (mg)
BW = body weight of all mammals in the test chamber (mg)
CA = concentration of hexane in arterial blood (mg/l)
CF = concentration of hexane in fat (mg/l)
CI = concentration of hexane in inhaled air (mg/l)
CL1 = concentration of hexane in liver (mg/l)
CL2 = concentration of methyl-n-butylketone in liver (mg/l)
CL3 = concentration of 2,5-hexanedione in liver (mg/l)
CR = concentration of hexane in rapidly perfused tissue (mg/l)
CS = concentration of hexane in slowly perfused tissue (mg/l)
CV = concentration of hexane in venous blood (mg/l)
CVF = concentration of hexane in venous blood leaving fat tissue (mg/l)
CVL = concentration of hexane in venous blood leaving liver (mg/l)
CVR = concentration of hexane in venous blood leaving rapidly perfused tissue (mg/l)
CVS = concentration of hexane in venous blood leaving slowly perfused tissue (mg/l)
CX = concentration of hexane in exhaled air (mg/l)
K = rate constant for the excretion of 2,5-hexanedione (1/hr)
KFO = rate constant for first order metabolism (mg/l)

TABLE 2.1 (continued)

KM1 = enzyme affinity for hexane (mg/l)
KM2 = enzyme affinity for methyl-n-butylketone (mg/l)
KM2I = constant for describing interference of metyl-n-butylketone on hexane metabolism (mg/l)
KM3 = enzyme affinity for 2,5-hexanedione (mg/l)
L1 = ratio of molecular weights of methyl-n-butylketone to hexane
L2 = ratio of molecular weights of 2,5-hexanedione to methyl-n-butylketone
PB = blood to air partition coefficient
PF = fat to blood partition coefficient
PL1 = hexane liver to blood partition coefficient
PL2 = methyl-n-butylketone liver to blood partition coefficient
PL3 = 2,5-hexanedione liver to blood partition coefficient
PR = rapidly perfused tissue to blood partition coefficient
PS = hexane slowly perfused tissue to blood partition coefficient
QC = cardiac output (l/hr)
QF = fat compartment blood flow rate (l/hr)
QL = liver blood flow rate (l/hr)
QP = alveolar ventilation rate (l/hr)
QR = rapidly perfused tissue flow rate (l/hr)
QS = slowly perfused tissue flow rate (l/hr)
RAM1 = rate that hexane metabolizes into methyl-n-butylketone (mg/hr)
RAM2 = rate that methyl-n-butylketone metabolizes into 2,5-hexanedione (mg/hr)
RAM3 = rate that methyl-n-butylketone metabolizes into other substances (mg/hr)
VF = volume of fat compartment (l)
VL = volume of liver compartment (l)
VMAX1 = maximum velocity of metabolism for hexane (mg/hr)
VMAX2 = maximum velocity of metabolism for methyl-n-butylketone (mg/hr)
VMAX3 = maximum velocity of metabolism for 2,5-hexanedione (mg/hr)
VR = volume of rapidly perfused tissue compartment (l)
VS = volume of slowly perfused tissue compartment (l)
VW = volume of distribution of 2,5-hexanedione (l)

TABLE 2.2 Parameter values and defining relationships

```
BW    = .3
CA    = (QC*CV +  CI*QP)/(QP/PB + QC)
CF    = AF/VF
CL1   = AL1/VL
CL2   = AL2/VL
CL3   = AL3/VL
CR    = AR/VR
CS    = AS/VS
CV    = (QF*CVF + QL*CVL + QR*CVR + QS*CVS)/QC
CVF   = AF/(VF*PF)
CVL   = AL1/(VL*PL1)
CVR   = AR/(VR*PR)
CVS   = AS/(VS*PS)
CX    = CA/PB
KM1   = .36
L1    = 1.186
L2    = 1.14
PB    = .8
PF    = 70.0
PL1   = 2.3
PL2   = 1.0
PL3   = 1.0
PR    = 4.0
PS    = 1.26
QC    = 4.13 = QF + QL + QS + QR
QF    = .04*QC
QL    = .3*QC
QP    = 3.85
QR    = .48*QC
QS    = .2*QC
RAM1  = KFO*CVL*VL + VMAX1*AL1/(VL*PL1*KM1*(1 + (AL2 + AL3)/(VL*KM2I)))
RAM2  = VMAX2*AL2/(AL2 + VL*PL2*KM2 + PL2*AL1/KM1)
RAM3  = VMAX3*AL2/(VL*PL2*KM3 + AL2)
VF    = .04*BW
VL    = .04*BW
VMAX1 = 1.8
VR    = .05*BW
VS    = .78*BW
VW    = .12
```

With the following relationships,

$$dAI = CI*QP*dt \tag{2.2}$$
$$dAX = CX*QP*dt \tag{2.3}$$
$$dAB = dCA*dt \tag{2.4}$$
$$\text{(amount entering from venous blood)} = QC*CV*dt \tag{2.5}$$
$$\text{(amount leaving with arterial blood)} = AC*CA*dt \tag{2.6}$$

equation (2.1) may be written as

$$CI*QP*dt + QC*CV*dt = CX*QP*dt + dAB + QC*CA*dt \tag{2.7}$$

Rewriting equation (2.7), we have

$$dAB = -QC*CA*dt - QP*CX*dt + CI*QP*dt + QC*CV*dt \tag{2.8}$$

Differentiating equation (2.4) with respects to t gives

$$dAB/dt = dCA/dt \tag{2.9}$$

Now differentiating equation (2.8) with respects to t and substituting in equation (2.9) gives

$$dCA/dt = -QC*CA - QP*CX + CI*QP + QC*CV \tag{2.10}$$

In the past, researchers at AFAMRL have noted that the concentration in CA reaches equilibrium rapidly in relation to the other compartments. This observation led to the assumption that dCA/dt is approximately zero. Hence, equation (2.8) becomes

$$QC*CA + QP*CX = CI*QP + QC*CV \tag{2.10}$$

Since CX = CA/PB, then equation (2.10) is written as

$$QC*CA + QP*CA/PB = CI*QP + QC*CV \tag{2.11}$$

or, after rearranging,

$$CA = (QC*CV + CI*QP)/(QP/PB + QC) \tag{2.12}$$

Fat, Slowly Perfused Tissue, and Rapidly Perfused Tissue Compartments. The compartments of fat, slowly perfused tissue and rapidly perfused tissue have mass balance equations of a similar form. The equation for fat will be developed first.

For fat, we have the following mass balance equation,

$$QF*CA*dt = QF*CVF*dt + dAF \tag{2.13}$$

As Mayberry points out, equation (2.13) says that for a small time interval dt, the amount of hexane entering the compartment through the arterial blood is equal to the amount of hexane leaving the compartment through venous blood plus the amount of hexane absorbed by the compartment.

Equation (2.13) is rewritten as

$$dAF/dt = QF*CA - QF*CVF \qquad (2.14)$$

or, since CVF = AF/(VF*PF), equation (2.14) becomes

$$dAF/dt = QF*(CA - AF/(VF*PF)) \qquad (2.15)$$

Equations (2.14) and (2.15) are in a form that may be implemented on the computer and solved using a numerical integration routine.

The differential equations are similarly derived for the slowly perfused tissue and rapidly perfused tissue. For the slowly perfused tissue, the equations are

$$dAS/dt = QS*(CA - CVS) \qquad (2.16)$$

or

$$dAS/dt = QS*(CA - AS/(VS*PS)) \qquad (2.17)$$

For the rapidly perfused tissue, the equations are

$$dAR/dt = QR*(CA - CVR) \quad (2.18)$$

or

$$dAR/dt = QR*(CA - AR/(VR*PR)) \quad (2.19)$$

Hexane in Liver Compartment. The mass balance equation for hexane gas in the liver is

$$QL*CA*dt = dAL1 + dAM1 + QL*AL1*dt/(VL*PL1) \quad (2.20)$$

where

QL*CA*dt = amount of hexane entering the liver compartment
dAL1 = amount of hexane absorbed by the liver tissue
dAM1 = amount of hexane metabolized into methyl-n-butylketone
QL*AL1*dt/(VL*PL1) = amount of hexane that leaves the liver compartment through venous blood

Equation (2.20) may be written as

$$dAL1/dt = QL*(CA - CVL) - dAM1/dt \quad (2.21)$$

Scientists at AFAMRL, however, have determined that

$$dAM1/dt = RAM1 = KFO*CVL*VL + \quad (2.22)$$
$$VMAX1*AL1/(VL*PL1*KM1*(1 + (AL2 + AL3)/(VL*KM2I)))$$

Substituting RAM1 and CVL = AL1/(VL*PL1) into equation (2.21) gives

$$dAL1/dt = QL*(CA - AL1/(VL*PL1)) - RAM1 \quad (2.23)$$

Methyl-n-butylketone in Liver Compartment. The mass balance equation for methyl-n-butylketone that is in the liver is

$$QL*AW1*dt/VW + dAM1*L1 = dAL2 + dAM2 + dAM3 + \quad (2.24)$$
$$QL*AL2*dt/(VL*PL2)$$

where

QL*AW1*dt/VW = amount of methyl-n-butylketone entering the liver compartment from the body water
dAM1*L1 = amount of hexane metabolized into methyl-n-butylketone and retained in liver
dAL2 = amount of methyl-n-butylketone absorbed by the liver tissue
dAM2 = amount of methyl-n-butylketone metabolized into 2,5-hexanedione
dAM3 = amount of methyl-n-butylketone metabolized into other substances
QL*AL2*dt/(VL*PL2) = amount of methyl-n-butylketone that is distributed to body water

Writing equation (2.24) as a differential equation, we have

$$-dAL2/dt = QL*AL2/(VL*PL2) - QL*AW1/VW - dAM1/dt*L1 + dAM2/dt + dAM3/dt \quad (2.25)$$

But, since

$$dAM1/dt = RAM1$$
$$dAM2/dt = RAM2 = VMAX2*AL2/(AL2 + VL*PL2*KM2 + PL2*AL1/KM1)$$
$$dAM3/dt = RAM3 = VMAX3*AL2/(VL*PL2*KM3 + AL2)$$

we may write equation (2.25) as

$$-dAL2/dt = QL*AL2/(VL*PL2) - QL*AW1/VW - RAM1*L1 + RAM2 + RAM3 \quad (2.26)$$

2,5-hexanedione in Liver Compartment. The mass balance equations for 2,5-hexanedione that is in the liver compartment is

$$QL*AW2*dt/VW + dAM2*L2 = dAL3 + QL*AL3*dt/(VL*PL3) \quad (2.27)$$

where

QL*AW2/VW = amount of 2,5-hexanedione entering from the body water
dAM2*L2 = amount of 2,5-hexanedione metabolized from methyl-n-butylketone and retained in liver
dAL3 = amount of 2,5-hexanedione absorbed by liver tissue
QL*AL3/(VL*PL3) = amount of 2,5-hexanedione distributed to body water

Writing equation (2.27) as a differential equation, substituting dAM2/dt = RAM2, and rewriting, we have

$$dAL3/dt = QL*AW2/VW + L2*RAM2 - QL*AL3/(VL*PL3) \qquad (2.28)$$

Methyl-n-butylketone in Body Water Compartment. The mass balance equation for the amount of methyl-n-butylketone in body water is

$$dAW1 = QL*CL2*dt/(VL*PL2) - QL*AW1*dt/VW \qquad (2.29)$$

where

AW1 = amount of methyl-n-butylketone in body water
QL*CL2*dt/(VL*PL2) = amount of methyl-n-butylketone entering from the liver
QL*AW1*dt/VW = amount of methyl-n-butylketone leaving the body water and entering the liver

Writing equation (2.29) as a differential equation, we have

$$dAW1/dt = QL*CL2/(VL*PL2) - QL*AW1/VW \qquad (2.30)$$

2,5-hexanedione in Body Water Compartment. The mass balance equation for 2,5-hexanedione in body water is

$$dAW2 = QL*CL3*dt/(VL*PL3) - QL*AW2*dt/VW - K*AW2*dt \qquad (2.31)$$

where

AW2 = amount of 2,5-hexanedione in body water
QL*CL3*dt/(VL*PL3) = amount of 2,5-hexanedione entering from the liver
QL*AW2*dt/VW = amount of 2,5-hexanedione leaving body water and entering the liver
K*AW2*dt = amount of 2,5-hexanedione excreted to the kidneys

Writing equation (2.31) as a differential equation, we have

$$dAW2/dt = QL*CL3/(VL*PL3) - QL*AW2/VW - K*AW2 \qquad (2.32)$$

Equation (2.32) marks the last of the eight differential equations that model the Open Chamber Hexane Model. Now, we must relate these differential equations to the measurements taken during the experiment. The next section describes the models of the measurements.

Measurement Models. During the experiment, researchers have collected measurements used for estimating the unknown parameters. One set of experimental data is the input chamber concentration level of hexane. The other three experimental data sets were extracted from the drug concentration levels inside the mammal. The observations include the hexane concentration level in the blood, the concentration level of methy-n-butylketone

in the body water, and the concentration level of 2,5-hexanedione in the body water. The three measurement models give the predicted values used for comparison with the experimental observations.

The first measurement model, concentration of hexane in the blood, is given by

$$y_1 = CA \tag{2.33}$$

where CA is defined by equation (2.12). The second measurement model, the concentration level of methyl-n-butylketone in body water, is given by

$$y_2 = 5*AW1 \tag{2.34}$$

Finally, the third measurement model, the concentration level of 2,5-hexanedione in body water, is given by

$$y_3 = 5*AW2 \tag{2.35}$$

Unknown Model Parameters

The values for seven of the parameters listed in Table 2.1 are unknown. In order that the Hexane Model be useful, these parameters must

be estimated. The researchers at AFAMRL have requested that, when estimated, the parameters satisfy certain constraints. These constraints ensure that the estimates will make physical sense. Table 2.3 displays the unknown parameters and their constraints.

TABLE 2.3 Unknown model parameters

2.4	≤	KF0	≤	4.4
.2	≤	VMAX2	≤	2.0
.1	≤	KM2	≤	10.0
1.0	≤	VMAX3	≤	5.0
.1	≤	KM3	≤	10.0
1.0	≤	KM2I	≤	1000.0
.1	≤	K	≤	.6

Experimental Data

The data was obtained from AFAMRL. Four experiments were run, each with a different time history of the input concentration level of hexane. Each experiment was started at a relative time point of zero. The data is given in Table 2.4.

TABLE 2.4(a) Experimental data: Run #1

Time (hrs)	*Input	*Hexane	*MNBK	*2,5-HD
6.0	1.8	1.3	.7	3.2
6.5	0.0	---	---	3.6
7.0	0.0	---	---	3.6
8.0	0.0	---	---	2.8
10.0	0.0	---	---	2.0
12.0	0.0	---	---	.8
14.0	0.0	---	---	.4
18.0	0.0	---	---	.2

TABLE 2.4(b) Experimental data: Run #2

Time (hrs)	Input	Hexane	MNBK	2,5-HD
.5	3.5	1.6	.8	---
1.0	3.5	1.4	.9	---
2.0	3.5	1.7	1.6	---
3.0	3.5	2.2	1.8	---
4.0	3.5	1.6	1.6	---
6.0	3.5	2.2	2.4	---
6.5	0.0	---	---	5.6
7.0	0.0	---	---	5.1
8.0	0.0	---	---	6.1
10.0	0.0	---	---	4.7
12.0	0.0	---	---	4.2

*Note: Input = input chamber concentration level (mg/l)
Hexane = hexane concentration level in blood (mg/l)
MNBK = concentration of methyl-n-butylketone in body water (mg/l)
2,5-HD = concentration of 2,5-hexanedione in body water (mg/l)

TABLE 2.4(c) Experimental data: Run #3

Time (hrs)	Input	Hexane	MNBK	2,5-HD
.5	10.6	1.6	.8	---
1.0	10.6	1.4	.9	---
2.0	10.6	1.7	1.6	---
3.0	10.6	2.2	1.8	---
4.0	10.6	1.6	1.6	---
6.0	10.6	2.2	2.4	---
6.5	0.0	---	1.9	5.6
7.0	0.0	---	---	5.1
8.0	0.0	---	---	6.1
10.0	0.0	---	---	4.7
12.0	0.0	---	---	4.2

TABLE 2.4(d) Experimental data: Run #4

Time (hrs)	Input	Hexane	MNBK	2,5-HD
.5	35.3	7.9	1.5	---
1.0	35.3	8.5	2.4	---
2.0	35.3	9.8	3.9	---
3.0	35.3	9.0	4.0	---
4.0	35.3	9.7	3.7	---
6.0	35.3	8.4	4.2	---
6.5	0.0	2.2	5.4	2.8
7.0	0.0	1.9	2.6	6.7
8.0	0.0	1.3	1.1	4.6
10.0	0.0	---	---	4.0
12.0	0.0	---	---	5.8
14.0	0.0	---	---	4.0

Summary of the Closed Chamber Hexane Model Equations

The model equations are

$$\dot{X}_1 = dAF/dt = QF*(CA - CVF)$$

$$\dot{X}_2 = dAL1/dt = QL*(CA - AL1/(VL*PL1)) - RAM1$$

$$\dot{X}_3 = dAL2/dt = -QL*AL2/(VL*PL2) + QL*CW1/VW + RAM1*L1 - RAM2 - RAM3$$

$$\dot{X}_4 = dAL3/dt = QL*AW2/VW + L2*RAM2 - QL*AL3/(VL*PL3)$$

$$\dot{X}_5 = dAW1/dt = QL*CL2/(VL*PL2) - QL*AW1/VW$$

$$\dot{X}_6 = dAW2/dt = QL*CL3/(VL*PL3) - QL*AW2/VW - K*AW2$$

$$\dot{X}_7 = dAS/dt = QS*(CA - CVS)$$

$$\dot{X}_8 = dAR/dt = QR*(CA - CVR)$$

The measurement equations are

$$y_1 = CA = (QC*CV + CI*QP)/(QP/PB + QC)$$

$$y_2 = 5*AW1$$

$$y_3 = 5*AW2$$

III. Background

System identification has long been an area of interest and application. Techniques of system identification are intended to help develop models that describe the phenomena of interest. These models are usually mathematical relationships among important variables. Typically, these models describe physical processes, although equations of more abstract processes are also popular. The models may range anywhere from a fully defined set of equations with perhaps a few unknown parameters to a model that is completely unspecified. However, the specification of the model and its unknowns will determine the results from estimation. Thus, consideration must be given to modelling the desired phenomena appropriately.

Another critical issue in system identification is that of deciding how to evaluate the agreement between the theoretical model and the observations. This measure of agreement will guide the selection of values for the unknown parameters. The values that give the optimal measure of agreement will be chosen as the estimates. Methods of selecting the estimates are usually

called optimization methods. Researchers must also be concerned with the collection of experimental data. Sometimes, control may be exercised over the phenomena of interest. In that case, researchers may be able to design experiments and collect data in a manner that will provide very precise estimates.

This chapter presents background material that may be useful in the identification of parameters of the Open Chamber Hexane Model. The topics presented are modeling, optimization and experimentation. Occasionally, some of the topics will be mentioned briefly. The reason is that each of the topics and many of their subtopics involve concepts that are very detailed and require much study to understand fully. Still, these topics are mentioned since they may prove useful in indicating where we might go to pursue further an important subject for future applications.

Stochastic Modeling

The Open Chamber Hexane Model presented in Chapter II is a deterministic model. The uncertainties that may be involved in the model have not been addressed. The deterministic model may be appropriate if the uncertainties are negligible. However, researchers at AFAMRL have indicated that modeling these uncertainties may be appropriate if at all possible in future applications.

Hence, a review of some techniques dealing with these uncertainties may be beneficial.

In the Hexane Model, uncertainties derive from three sources. The first source stems from the fact that not all is known about the true metabolic and distribution processes of drugs in the mammal. In addition, not all of the processes involved are being modelled. Noise variables may be used to account for the underlying processes not included in the model. The second source of uncertainty stems from the fact that measurement data itself is corrupted by the measuring equipment and procedures followed during the experiment. Finally, the results are expected to vary since each mammal of the same species does not possess the same physiological characteristics. Estimating parameters of dynamic models in the presence of noise requires knowledge about statistics and stochastic processes. This section reviews some of these concepts for both linear and nonlinear models.

Linear Dynamic Stochastic Models. A linear dynamic system with time-invariant parameters and no noise may be written as

$$\dot{\underline{X}}(t) = \underline{F}*\underline{X}(t) + \underline{b}*U(t) \qquad (3.1a)$$

$$\underline{Z}(t) = \underline{h}*\underline{X}(t) \qquad (3.1b)$$

For the case of linear, time-invariant pharmacokinetic models,

$\underline{X}(t)$ represents the drug concentration levels in each compartment. $\underline{U}(t)$ is the hexane concentration in the air and $\underline{Z}(t)$ represents the measurements of the model. $\underline{F}$, $\underline{b}$, and $\underline{h}$ are constant matrices that describe the relationship between $\underline{X}(t)$, $\underline{U}(t)$, and $\underline{Z}(t)$.

One way to account for model uncertainties is to add noise terms to the noise free model. Adding noise terms to the equations of (3.1) gives

$$\dot{\underline{X}}(t) = \underline{F}*\underline{X}(t) + \underline{b}*U(t) + \underline{G}*\underline{n}_1(t) \qquad (3.2a)$$

$$\underline{Z}(t) = \underline{h}*\underline{X}(t) + \underline{n}_2(t) \qquad (3.2b)$$

In general, for any noise terms $\underline{n}_1(t)$ and $\underline{n}_2(t)$, the model may not be directly solvable. However, if $\underline{n}_1(t)$ and $\underline{n}_2(t)$ are assumed to be white gaussian noise processes, then solutions for $\underline{X}(t)$ and $\underline{Z}(t)$ are obtained in a relatively straight forward manner.

To fully characterize $\underline{n}_1(t)$ as white noise, we first note that it is a continuous function of time. For this case, $\underline{n}_1(t)$ has infinite variance and yet it is uncorrelated in time. It has a mean of zero and a constant power spectrum. Since its power spectrum is constant, white noise is typically specified by this constant, say $\underline{Q}$. Thus, $\underline{n}_1(t)$ may be specified completely as a white noise process with a power spectrum of strength $\underline{Q}$.

We also note that

$$\int_0^t \underline{n}_1(t)*dt = \underline{Br}(t) \tag{3.3}$$

where

$\underline{Br}(t)$ = brownian motion process

The noise term $\underline{n}_2(t)$ differs from $\underline{n}_1(t)$ in that it is a discrete function of time. In this case $\underline{n}_2(t)$ is completely specified by a mean of zero and a covariance matrix $\underline{R}$.

The solution to the system of stochastic differential equations (3.2a) becomes

$$\underline{X}(t) = \underline{W}(t,t_0)*\underline{X}(t_0) + \int_{t_0}^t \underline{W}(t,s)*\underline{b}*U(s)*ds + \int_{t_0}^t \underline{W}(t,s)*\underline{G}*d\underline{Br}(s) \tag{3.4}$$

where

$\underline{W}(t,t_0)$ = solution to the differential equation

$$d(\underline{W}(t,t_0))/dt = \underline{F}*\underline{W}(t,t_0)$$

and $\underline{W}(t_0,t_0) = \underline{I}$

The solution $\underline{X}(t)$ is a gaussian process completely characterized by its mean and covariance matrix

$$\text{mean} = \underline{X}(t) = \underline{W}(t,t_0)*\underline{X}(t_0) + \int_{t_0}^{t} \underline{W}(t,s)*\underline{b}*U(s)*ds \qquad (3.5a)$$

$$\begin{matrix}\text{covariance} \\ \text{matrix}\end{matrix} = \underline{P}(t) = \underline{W}(t,t_0)*\underline{P}(t_0)*\underline{W}(t,t_0)^T + \qquad (3.5b)$$

$$\int_{t_0}^{t} \underline{W}(t,s)*\underline{G}*\underline{Q}*\underline{G}^T*\underline{W}(t,s)^T*ds$$

To obtain the solution (3.4), all of the values in the matrices $\underline{F}$, $\underline{b}$, $\underline{G}$, and $\underline{Q}$ must be known. However, in many applications not all of the values are known. In such cases, parameter estimation techniques are used to estimate these values.

In the simple case with unknown values only in $\underline{F}$, Eykhoff mentions that parameter estimation is still a nonlinear problem. "This implies that all approaches to this problem will have the characteristics of the model-adjustment technique, i.e. they will be of an iterative type." (EYKH74: 446-7) So, even for this simple case, no closed form solution can be found generally for estimating the unknown parameters.

Even though closed form solutions for the parameter estimates may not be available, solutions may be found with numerical techniques. Unfortunately, not much has been said in the literature

about the exact probability distributions of the estimates. This makes it difficult to determine how precise our estimates are. However, Goodwin and Payne provide an equation that may be used to estimate the precision of the estimates. (GOOD77: 99-102) The Cramer-Rao lower bound is another approximation to the precision of the estimates. (EYKH74: 27)

Nonlinear Dynamic Stochastic Models. A typical representation of nonlinear stochastic differential equations is given by

$$\dot{\underline{X}} = \underline{F}(\underline{X}(t),\underline{U}(t),\underline{q}) + \underline{G}*\underline{n}(t) \qquad (3.6)$$

In general, even when the unknown parameters q are assumed known, the solution $\underline{X}(t)$ to this equation is still extremely difficult to find. Usually many approximations must be made to the equation in order to solve it. Springer reports, however, that the theory of H-functions may be useful in dealing with such nonlinear estimation problems. (SPRI79: 8) Unfortunately, it was not possible to investigated further the use of H-functions for this thesis effort.

A technique that may be useful in estimating the parameters of nonlinear as well as linear models is the jacknife. A version of the jacknife was developed by Quenouille (QUEN56) and then later developed by Tukey (TUKE58). Mostellor and Tukey state that

> The name "jacknife" is intended to suggest the broad usefulness of a technique as a substitute for specialized tools that may not be available, just as the Boy Scout's trusty tool serves so variedly. The jacknife offers ways to set sensible confidence limits in complex situations. (MOST77: 133)

Because of its wide generality in estimating parameters and their variances, the jacknife technique may prove to be a valuable tool in system identification. However, because of time constraints, it was not possible to apply the jacknife to the Hexane Model.

Optimization

Numerous techniques have been developed for numerical optimization. Several of these techniques are discussed by Bard (BARD74) and Eykhoff (EYKH74). Other techniques may be found by searching through the many texts and articles dealing with optimization and mathematical programming. Only a few of these techniques will be mentioned in this section.

Most optimization methods useful in parameter estimation fall under the categories of local and global optimization. Also, optimization techniques exist for dealing with the added complexity of constraints.

Parameter estimation of pharmacokinetic models requires

the techniques to handle global optimization with constraints. However, global optimization techniques and methods to handle constraints both typically build upon the techniques of local optimization. Therefore, it is fitting to examine first some of the literature dealing with unconstrained local optimization.

Unconstrained Local Optimization. Of all the numerical optimization methods in existence, those dealing with unconstrained local optimization are probably the most numerous and widely discussed. However, only a few of the unconstrained local optimization techniques will be discussed. In order to discuss these techniques, the following notations will be used:

$\underline{q}$ = the vector of unknown parameters
E = the error function

The objective of parameter estimation is to minimize the error function E where E is a measure of the distance between the observations and the model's predicted values.

Steepest Descent Method. The Steepest Descent algorithm is given by (EYKH74: 158)

$$\underline{q}(i+1) = \underline{q}(i) - J * \partial E/\partial \underline{q} \Big|_{\underline{q} = \underline{q}(i)} \quad , J>0 \qquad (3.7)$$

This algorithm updates the estimate of $\underline{q}(i)$ each iteration with a correction factor, $J * \partial E/\partial \underline{q} \Big|_{\underline{q} = \underline{q}(i)}$. For sufficiently small J, this updated value will reduce the value of E. The gradient $\partial E/\partial \underline{q}$ indicates the direction to change $\underline{q}(i)$ in order to reduce E by a maximum amount. Unfortunately, this maximum reduction of E may occur only for very small excursions away from $\underline{q}(i)$. Without further knowledge about the function E, we cannot be sure that a large change of $\underline{q}(i)$ in the direction $\partial E/\partial \underline{q} \Big|_{\underline{q}=\underline{q}(i)}$ decreases E at all.

The constant J should be chosen so that the correction will yield a decrease in E for each iteration. If J is too large, it is possible that the algorithm will overshoot the minimum value. On the other hand, if J is too small, the algorithm may move too slowly towards the minimum and waste computer resources. To choose the best value for J, we may need to try many values and choose the value that does well in reducing the error.

The method of Steepest Descent does have the advantage of guaranteed convergence to a local minimum (EYKH74: 161). This is not necessarily true for other methods. The disadvantage of the Steepest Descent method is that it may not converge as rapidly as these other methods.

Newton-Raphson Method. This algorithm is given by

$$\underline{q}(i+1) = \underline{q}(i) - \left[\partial^2 E/\partial \underline{q}\partial \underline{q}^T\right]^{-1}_{\underline{q}=\underline{q}(i)} * \partial E/\partial \underline{q}\Big|_{\underline{q}=\underline{q}(i)} \qquad (3.8)$$

This algorithm can be related to the Steepest Descent method by letting $J = \left[\partial^2 E/\partial \underline{q}\partial \underline{q}^T\right]^{-1}_{\underline{q}=\underline{q}(i)}$. With this added information of second derivatives, the Newton-Raphson method generally updates q(i) at each iteration with greater reduction in the error function E. But, to ensure such greater reduction, the Newton-Raphson method should have a starting value close to the minimum.

As noted by Eykhoff, "evaluation of the second derivative is quite a troublsome job." (EYKH74: 161) However, if the error function E is a weighted least squares error function, then the simpler Gauss-Newton method may be used to approximate the Newton-Raphson method.

Gauss-Newton Method. For a weighted least squares error function, the Newton-Raphson method can be approximated by the Gauss-Newton method. Eykhoff provides the derivation for the case of continuous measurements. For this case, the error function is

$$E = \int_0^\tau \underline{e}(t)^T * \underline{Q} * \underline{e}(t) * dt \qquad (3.9)$$

where

$\underline{e} = \underline{O}(t) - \underline{y}(\underline{q},t)$

$\underline{Q}$ = a positive-definite, symmetric weighting

$\underline{O}(t)$ = measurement data

$\underline{y}(\underline{q},t)$ = the model's predicted values

From the error function, we have the following:

$$\partial E/\partial \underline{q} = -\int_0^{\tau} \partial \underline{y}(\underline{q},t)^T/\partial \underline{q} * \underline{Q} * \underline{e} * dt \tag{3.10}$$

$$\partial^2 E/\partial \underline{q} \partial \underline{q}^T = \int_0^{\tau} \partial \underline{y}(\underline{q},t)^T/\partial \underline{q} * \underline{Q} * \partial \underline{y}(\underline{q},t)/\partial \underline{q}^T * dt \tag{3.11}$$

Substituting equations (3.10) and (3.11) into (3.8) gives the following Gauss-Newton algorithm (EYKH74: 161)

$$\underline{q}(i+1) = \underline{q}(i) + \left[\int_0^{\tau} (\partial \underline{y}^T/\partial \underline{q}) * \underline{Q} * (\partial \underline{y}/\partial \underline{q}^T) * dt\right]^{-1}_{\underline{q}=\underline{q}(i)} * \left[\int_0^{\tau} (\partial \underline{y}^T/\partial \underline{q}) * \underline{Q} * \underline{e} * dt\right]_{\underline{q}=\underline{q}(i)} \tag{3.12}$$

The advantage of this algorithm over the Newton-Raphson algorithm is that no second derivatives need to be calculated.

Hence, the computations are simplified. Unlike the method of Steepest Descent, however, this method does not guarantee convergence to a local minimum. On the other hand, when close to the minimum, the Gauss-Newton method converges faster than the Steepest Descent method.

Box-Kanemasu Interpolation Method. A particular algorithm described by Beck and Arnold is the Box-Kanemasu algorithm. The Box-Kanemasu algorithm is simply a modification of the Gauss-Newton method. (BECK77: 362) Beck and Arnold report that the Box-Kanemasu algorithm is superior to most other optimization techniques. They also point out that

> Bard [Bard, p. 111] appears to favor a modification of the Box-Kanemasu method which he calls the interpolation-extrapolation method. (BECK77: 375)

Furthermore, they state that the

> Box-Kanemasu method is recommended in order to be more certain of finding the parameter values minimizing S the error function, even though in some cases the Gauss method would be more efficient. (BECK77: 378)

Beck and Arnold conclude that the Gauss-Newton method and the Box-Kanemasu method both work well in parameter estimation

problems.

Conjugate Gradient Method. The Conjugate Gradient method is presented by Fletcher and Reeves (FLET64). Chattergy and Wismer report that the Conjugate Gradient method converges faster than the Steepest Descent method near the optimum point (CHAT78: 332). However, Maybeck points out that "the literature reports certain undesirable numerical characteristics of this algorithm for the parameter estimation application." (MAYB82a: 82) It appears that perhaps not much can be said about the performance of the Conjugate Gradient method unless we implement it specifically on the model of interest aand evaluate its performance.

Derivative-Free Methods. The optimization techniques mentioned so far required that at least the derivative of the error function be calculated. Sometimes, however, it may be too difficult to find analytically the derivatives. In this case, a derivative-free method may prove useful. Two derivative-free techniques described in this section are the method of finite differences and the method of direct search.

With the method of finite differences, the algorithms discussed previously may still be used. The only modification involves approximating the derivatives in these algorithms. For example, all of the algorithms required that the gradient $\partial E/\partial q$ be known. A finite difference approximation to this vector is composed of

elements found by (BARD74: 117)

$$\partial E/\partial q_i \cong \Delta E/\Delta q_i \tag{3.13}$$

where

$$\Delta E/\Delta q_i = \left[E(q_1, q_2, \cdots, q_i+\delta_i, \cdots, q_n) - E(q_1, q_2, \cdots, q_i, \cdots, q_n)\right]/\delta_i \tag{3.14}$$

and δ_i is sufficiently small

Similar approximations can also be made for the second derivative.

Other derivative-free techniques are the direct search techniques. These techniques include the first and second Posell methods, Hooke and Jeeves pattern search, Rosenbrock's method, and the simplex method of Nelder and Mead, to name a few. (BARD74: 120)

Direct search methods have performed well in some cases, but Bard notes their inadequacy for parameter estimation. Specifically, Bard states

> Our own experience, however, has been disappointing; gradient methods, even using finite difference approximations have outperformed direct search methods on all but the most trivial parameter estimation problems, both in reliability and speed of convergence. (BARD74: 119-120)

In addition, Banks states that

> These methods, which make use of only functional evaluations, are attractive in some cases if one suspects that the function J to be minimized is not smooth, but they are slow and usually quite inefficient when highly accurate solutions are desired. Furthermore, they have been developed heuristically and no proofs of convergence have been given. (BANK80: 13-14)

In light of these comments, no attempt is made to explain in detail the direct search algorithms. The reader may consult the bibliography given by Bard for further references to these methods.

Unconstrained Global Optimization. The optimization methods discussed up to this point seek only to find the local optimum of the objective function. As a result, the estimate obtained by these methods may be a local minima and not global. In an attempt to correct these deficiencies, global optimization methods have been developed. No known technique can guarantee a globally optimal solution. However, these techniques will increase the chances of obtaining a global optimum.

Bard explains that most of the local minimization techniques will reach a global minimum provided they have appropriate starting values. (BARD74: 120) Therefore, a scheme for selecting good starting values should increase the chance of finding the global

minimum. Two such schemes explained by Bard are the grid search and the random search methods.

In the grid search method, a feasible region is first defined. This usually requires aprior knowledge about the model parameters. Typically, this feasible region is represented by upper and lower bounds of the unknown parameters. The feasible region then becomes rectangular. We conduct a grid search by selecting many points in the feasible region and evaluating the error function at each of the points. The point that has the smallest error function value is then used as the starting value. (BARD74: 121)

In the random search, test points are selected randomly. Then the point that has the smallest value in the objective function is used as the starting value. (BARD74: 121)

Variations of both the grid search and random search may be developed. For example, instead of using only one point for the starting value, we may use three points. Then an optimization algorithm may be applied with each of these values as starting values. Clearly, if all three solutions are equal, then we may be confident that the estimate is a global minimum. However, if the three solutions differ, then this indicates that many local minimums exist.

Another algorithm given by Bremermann also attempts to

obtain the global optimum. (BREM70) This method uses random search schemes in conjunction with interpolation of the objective function with a fourth degree polynomial. Lehman Stark report that with twelve test functions, the Bremermann algorithm was

> Faster than fourteen other algorithms when used on parameter spaces of dimension greater than four ... . Additionally, the random search has the advantage of global optimization: the program does not get stuck at local extrema, as gradient-search techniques are prone to do. (LEHM81: 117-118)

We should note that this statement errs in implying that this algorithm finds the global optimum. Rather, the algorithm at most only increases the chance of finding the global optimum.

Constrained Optimization. As indicated by the researchers of AFAMRL, the unknown parameters of the Hexane Model must satisfy certain inequality constraints. Thus, methods must be explored that ensure our estimates will satisfy those constraints. Chattergy and Wismer explain that (CHAT78: 163)

> There are many algorithms which have been proposed to solve constrained optimization problems using gradient techniques. Although these algorithms are too numerous to attempt a comprehensive treatment here, they can generally be divided into two categories:
>
> (1) boundary-following methods and
> (2) penalty-function methods.

Under the category of boundary following methods are the method of feasible directions and the gradient-projection method. For a further discussion of these methods, the reader may refer to Rosen (ROSE60; ROSE61) and Zoutendijk (ZOUT60).

The penalty-function methods for handling constraints are relatively simple. Penalty functions are used "to convert constrained optimization problems into unconstrained problems. Once the unconstrained problem is formulated, direct methods for solving this type of problem can be employed." (CHAT78: 197) Thus, the penalty-function methods have the advantage that the unconstrained optimization methods may be applied directly without modification.

Experimental Design for Dynamical Systems

Goodwin and Payne state that "For dynamic systems, experiment design includes choice of input and measurement points, test signals, sampling instants and presampling filters." (MEHR76: 252) These topics each appear to be relatively complex. A detailed investigation of experimental design procedures was not possible within the time constraints of this research. Instead, this section will provide a guide to some of the literature on experimental design for dynamical systems. The two topics that will be discussed in this section are (1) input design and (2) choice of sampling

instants.

Sinha and Kuszta describe three methods for the optimal design of inputs. They are (SINH83: 230)

a) method based on properties of Fisher's information matrix

b) method based on system sensitivity function optimization

c) method based on Gagliardi theorem - the "direct" method

In addition to these methods are input designs that aid in discriminating among many possible models. Together, these topics form a large part of the methods for input design.

The method involving Fisher's information matrix theory is sometimes referred to as the frequency domain design of input signals. (SINH83: 231) This method is also explained by Mehra (MEHR76: 211-229) and Goodwin and Payne (GOOD77: 133-157). Sinha and Kuszta note that Fisher's information matrix approach pertains to linear systems only.

The method using sensitivity functions may also be used to design the inputs to the model. Sensitivity functions are defined as $X_{ij} = \partial n_i / \partial q_j$ where n_i is a state variable and q_j is an unknown parameter. Beck and Arnold explain how the

sensitivity functions affect the convergence of the Gauss-Newton method. In particular, the matrix of sensitivity functions should be invertible near the region of the minimum. Should the determinant of the sensitivity matrix become small, then "The minimum point will not be very pronounced." (BECK77: 347) In this case, we might expect

> slow convergence of the Gauss method. For this reason it is important to examine the sensitivity coefficients over the region of interest. (BECK77: 348)

Furthermore,

> For effective nonlinear estimation, the careful examination of these sensitivity coefficients is imperative. (BECK77: 349)

A method of using sensitivity functions to design inputs is explained by Lehman and Stark. They recommend that normalized plots of the sensitivity functions be compared. From these plots, we know which state variables are affected the most by the unknown parameters at any time. (LEHM81: 113-117) Hence, the most precise estimates may be gained by gathering data when the sensitivities are the largest. Beck and Arnold describe how we might normalize the sensitivity functions. First, let X_{ij} be

the sensitivity function of the parameter q_j at time i. Also, n_i represents state variables and $\sigma_k(i)$ is the standard deviation of the k^{th} measurement at time i.

For single response cases with approximately constant standard deviations of the measurements it is convenient to examine

$$X'_{ij} = q_j * X_{ij} = q_j * \partial n_i / \partial q_j$$

Note that X'_{ij} has the units of n. Then the magnitude of each sensitivity can be compared with the others as well as with n itself.

For multiresponse cases it is often more meaningful to plot

$$X^+_{kj}(i) = (q_j / \sigma_k(i)) * (\partial n_k(i) / \partial q_j)$$

which is dimensionless. (Note i refers to "time", j to parameter, and k to response.)

Choosing inputs to maximize the sensitivities may be considered as a mathematical optimization problem. Using calculus of variations techniques, the problem is reduced to a two-point boundary value problem. Mehra (MEHR76: 211-249) and Sinha and Kuszta (SINH83: 235-237) examine the methods of input optimization for linear systems. Kalaba and Spingarn consider the case for nonlinear systems. (KALA82: 225-379)

Sinha and Kuszta provide a third approach to input optimization known as "the direct method of optimal input design." (SINH83: 237-258)

This method is developed only for linear time invariant systems. Goodwin and Payne provide a good development on input optimization. (GOOD77: 124-157)

The input optimization topics have so far

> Been concerned with the design of experiments for accurate parameter estimation within a model of specified structure. However, it is sometimes the case that there are two or more rival models and the purpose of the experiment may be to determine which, if any, of the models are adequate. (GOOD77: 167)

The topic of experimental design for model discrimination is considered by Bard (BARD74: 266-269), Beck and Arnold (BECK77: 464-473), and Goodwin and Payne (GOOD77: 167-172).

A final topic under experimental design considered in this chapter is the choice of sampling intervals. Goodwin and Payne state in the book edited by Mehra that

> for those problems where the choice of sampling instants and pre-sampling filters does arise, it has been recognized that this choice often has a significant effect on the information return from the experiment ... . The choice is particularly critical when the available computer storage and analysis time are limited. In these cases, the experiment should be designed to maximize the average information content of each sample. (MEHR76: 252)

The choice of sampling intervals may therefore be an important consideration for pharmacokinetic models since experiments are time limited. Goodwin and Payne discuss some methods in choosing sampling intervals, although these methods seem to apply only to linear systems. (GOOD77: 157-167; MEHR76: 251-287)

IV. Computer Algorithm Development for Parameter Estimation

Some of the parameter estimation methods discussed in Chapter III are developed in this chapter. Specifically, the optimization algorithms which were implemented on the computer are described. The model being considered is the deterministic representation of the Open Chamber Hexane Model presented in Chapter II. Parameter estimation of deterministic models has been the approach taken by AFAMRL in the past and is the approach they currently recommend now.

To develop the optimization routines, the error function was first defined. Once the error function was defined, computer algorithms were then designed and programmed to estimate the parameters. Next, the computer algorithms were tested. Once they were verified to work correctly, the computer programs were then compared.

Weighted Least Squares Criterion

The error function used for estimation is the weighted

least squares function. The primary consideration in this choice is the approval of the sponsors themselves. However, in addition to meeting AFAMRL's approval, this error function has another advantage. It does not require any statistical assumptions. (EYKH74: 39) This is important since the noises in the Hexane Model are not considered in this thesis effort.

Specifically, the weighted least squares error function used for parameter estimation is given by

$$E = \sum_{i=1}^{4} \sum_{j=1}^{3} \sum_{k=1}^{15} \left[(O_{ij}(k) - y_{ij}(k)) / O_{ij}(k) \right]^2 \qquad (4.1)$$

where

i = index over the four experimental runs
j = index over the three measurements
k = index over the fifteen observation time points
$O_{ij}(k)$ = experimental observations
$y_{ij}(k)$ = predicted values

One important issue in evaluating the error function is that of finding $y_{ij}(k)$. As shown in Chapter II, $y_{ij}(k)$ is derived from the solution of the differential equations of the Hexane Model. A great deal of Mayberry's work dealt with the solution of the differential equations of the pharmacokinetic models. A major problem noted by Mayberry is that the pharmacokinetic

models of interest are stiff. The concept of stiffness in differential equations is not examined in this thesis. Instead, the interested reader may refer to Mayberry's thesis. We do note here that stiff differential equations require special numerical integration techniques in order to provide adequate and efficient solutions. One of Mayberry's recommendations was that the IMSL routine DGEAR be used to solve the stiff differential equations. Thus, for the Hexane Model, DGEAR was used to evaluate the predicted values for $y_{ij}(k)$ in the error function.

Developing the Optimization Algorithm

Of the many optimization algorithms discussed in Chapter II, the Steepest Descent and the Gauss-Newton methods were the ones implemented on the computer. The Steepest Descent algorithm was selected because of its simplicity and its guarantee of convergence to a local minimum. The Gauss-Newton method, on the other hand, was selected because of some of the more favorable comments it received from the literature. Another method implemented on the computer has been named by the author as the Scalar Gauss-Newton method. Together, these three algorithms were programmed on the computer using the weighted least squares error function.

Steepest Descent Method. As mentioned in Chapter III, the Steepest Descent method updates its estimated parameters

according to the equation

$$\underline{q}(i+1) = \underline{q}(i) - J*\partial E/\partial \underline{q}\Big|_{\underline{q}=\underline{q}(i)} \tag{4.2}$$

With a step size J specified, the algorithm then begins from some initial value $\underline{q}(0)$ provided by the user. The only other value required for each iteration is $\partial E/\partial \underline{q}\Big|_{\underline{q}=\underline{q}(i)}$.

One approach to computing $\partial E/\partial \underline{q}$ follows by first defining

$$e_{ij}(k,q) = (O_{ij}(k) - y_{ij}(k,\underline{q}))/O_{ij}(k) \tag{4.3}$$

Thus, the error function may be written as

$$E(\underline{q}) = \sum_{i=1}^{4} \sum_{j=1}^{3} \sum_{k=1}^{15} (e_{ij}(k,\underline{q}))^2 \tag{4.4}$$

Differentiating equation (4.4) with respect to q_m, we see that

$$\partial E(\underline{q})/\partial q_m = \sum_{i=1}^{4} \sum_{j=1}^{3} \sum_{k=1}^{15} 2*e_{ij}*(\partial e_{ij}(k,\underline{q})/\partial q_m) \tag{4.5}$$

Differentiating equation (4.3) with respects to q_m, we see that

$$\partial e_{ij}(k,\underline{q})/\partial q_m = (-\partial y_{ij}(k,\underline{q})/\partial q_m)/O_{ij}(k) \qquad (4.6)$$

Substituting equation (4.6) into equation (4.5), we have

$$\partial E(\underline{q})/\partial q_m = \sum_{i=1}^{4}\sum_{j=1}^{3}\sum_{k=1}^{15} 2*e_{ij}*(-\partial y_{ij}(k,\underline{q})/\partial q_m)/O_{ij}(k) \qquad (4.7)$$

Hence, from equation 4.7, we now see that the computation of $\partial E(\underline{q})/\partial \underline{q}$ reduces to the computation of $\partial y_{ij}(k,\underline{q})/\partial q_m$ and e_{ij}.

Before evaluating $\partial y_{ij}(k,\underline{q})/\partial q_m$, we first recall that $y_{ij}(k,\underline{q})$ is defined by equations (2.33), (2.34), and (2.35). In other words, the measurements $y_{ij}(k,\underline{q})$ are related to the state variables $X_{nj}(k,\underline{q})$. To evaluate $\partial y_{ij}(k,\underline{q})/\partial \underline{q}$, we thus need to evaluate $\partial X_{nj}(k,\underline{q})/\partial \underline{q}$. The procedure for doing this is to first start with the original differential equations of the Hexane Model. This is given by

$$\dot{X}_{nj}(k,\underline{q}) = f_n(\underline{X},k,\underline{q}) \qquad (4.8)$$

Now, differentiating equation (4.8) with respect to each of the unknown parameters, we have

$$\partial(\dot{X}_{nj}(k,\underline{q}))/\partial q_m = \partial f_n(\underline{X},k,\underline{q})/\partial q_m \tag{4.9}$$

But,

$$\partial\dot{X}_{nj}(k,\underline{q})/\partial q_m = d(\partial X_{nj}(k,\underline{q})/\partial q_m)/dt \tag{4.10}$$

Thus, the sensitivity function $\partial X_{nj}(k,\underline{q})/\partial q_m$ may be expressed in terms of the differential equation

$$d(\partial X_{nj}(k,\underline{q})/\partial q_m)/dt = \partial f_n(\underline{X},k,\underline{q})/\partial q_m \tag{4.11}$$

The significance of equation (4.11) is that the solution to it is the sensitivity function which can be evaluated with the same numerical integration routine used to evaluate the differential equations of the Hexane Model. However, a problem with equation (4.11) arises when we consider the number of equations it represents. To use equation (4.11), we must differentiate each of the 8 equations $f_n(\underline{X},k,\underline{q})$ 7 times the 7 unknown parameters. This gives 56 differential equations that must be derived. Had $f_n(\underline{X},k,\underline{q})$ been linear, deriving the 56 differential equatoons may not have been difficult. However, since the Hexane Model is nonlinear, the derivation

of the 56 differential equations is very tedious. Thus, another method for evaluating $\partial E(\underline{q})/\partial \underline{q}$ was used.

The values for $\partial E(\underline{q})/\partial \underline{q}$ were approximated using the finite difference method presented in Chapter III. Although this method is only an approximation, it has the advantage that no additional differential equations were required. Thus, only the original model equations were needed to evaluate $\partial E(\underline{q})/\partial \underline{q}$.

As implemented on the computer, the Steepest Descent method accepts the new value $\underline{q}(i+1)$ as the current estimate only if it produces an error sum of squares value less than that of $\underline{q}(i)$. If $\underline{q}(i+1)$ is rejected, the step size J is adjusted to a smaller value and the iteration begins once again. However, once J becomes less than some very small value, the iteration stops since we are close to the local minimum.

To satisfy the boundary constraints placed on the parameters, additional logic was included into the computer program. When outside its limits, the parameter is replaced by its constraint value. Although this method seems to work well for the Hexane Model, there exist other modifications to the Steepest Descent algorithm that will enable it to deal with the constraints. The algorithm implemented on the computer is described in Figure 4.1.

Steepest Descent Algorithm

```
with a starting point q , evaluate ssq, the sum of squares error
DO WHILE ((step size J .GT. .000001) .AND. (counter .LE. max_count)
            .AND. (at least one improvement in the last 3 iterations))
   FOR i=1 to 7 DO
      q_temporary = q_i
      q_i = 1.00001*q_i
      evaluate ssq_new for the new vector q
      q_i = q_temporary
      ΔE/Δq_i = (ssq_new - ssq)*100000/q_i
      q_test_i = q_i - J*ΔE/Δq_i
      IF (q_test_i .LT. lowerbound_i) THEN
         q_test_i = lowerbound_i
      ELSE IF (q_test_i .GT. upperbound_i) THEN
         q_test_i = upperbound_i
      ENDIF
   ENDFOR i
   evaluate ssq_test for the new estimates q test
   IF (ssq_test .LT. ssq) THEN
      FOR i=1 to 7 DO
         q_i = q_test_i
      ENDFOR i
      ssq = ssq_test
      record that an "improvement" occurred this iteration
   ELSE
      record that "no improvement" occurred this iteration
      reduce J to J/10
   ENDIF
   increment counter
ENDWHILE
the final estimate is q with a sum of squares value ssq
```

FIGURE 4.1 Steepest Descent Algorithm

Gauss-Newton Method. To derive the Gauss-Newton algorithm for the Hexane Model, we start with the error function

$$E(\underline{q}) = \sum_{i=1}^{4} \sum_{j=1}^{3} \sum_{k=1}^{15} \left(e_{ij}(k,\underline{q})\right)^2 \qquad (4.4)$$

Next, a first order Taylor series approximation to $(e_{ij}(k,\underline{q}))^2$ is substituted into equation (4.4) to get

$$E(\underline{q}) = \sum_{i=1}^{4} \sum_{j=1}^{3} \sum_{k=1}^{15} \left[e_{ij}(k,\underline{q}^o) + \sum_{m=1}^{7} \left(\partial e_{ij}(k,\underline{q}^o)/\partial q_m\right) * \Delta q_m \right]^2 \qquad (4.13)$$

where

$$\Delta q = q_m - q_m^o$$

q_m^o = some nominal value

Now we minimize the error function by taking derivatives with respect to $\underline{q}$ and setting the result to zero. This gives

$$E(\underline{q})/\, q_n = \sum_{i=1}^{4} \sum_{j=1}^{3} \sum_{k=1}^{15} 2 * \left[e_{ij}(k,\underline{q}^o) + \sum_{m=1}^{7} \left(\partial e_{ij}(k,\underline{q}^o)/\partial q_m\right) * \Delta q_m \right] * \partial e_{ij}(k,\underline{q}^o)/\partial q_n \qquad (4.14)$$

$$= 0 \qquad \text{for } n = 1, 2, \ldots, 7$$

Dividing equation (4.14) by 2 and rewriting, we then have

$$\sum_{i=1}^{4}\sum_{j=1}^{3}\sum_{k=1}^{15} -e_{ij}(k,\underline{q}^{o})*(\partial e_{ij}(k,\underline{q}^{o})/\partial q_{n}) = \tag{4.15}$$

$$\sum_{i=1}^{4}\sum_{j=1}^{3}\sum_{k=1}^{15} (\partial e_{ij}(k,\underline{q}^{o})/\partial q_{n})* \sum_{m=1}^{7} (\partial e_{ij}(k,\underline{q}^{o})/\partial q_{m})*\Delta q_{m}$$

But, equation (4.15) may be rearranged to get

$$\sum_{i=1}^{4}\sum_{j=1}^{3}\sum_{k=1}^{15} -e_{ij}(k,\underline{q}^{o})*(\partial e_{ij}(k,\underline{q}^{o})/\partial q_{n}) = \tag{4.16}$$

$$\sum_{i=1}^{4}\sum_{j=1}^{3}\sum_{k=1}^{15}\sum_{m=1}^{7} (\partial e_{ij}(k,\underline{q}^{o})/\partial q_{m})*(\partial e_{ij}(k,\underline{q}^{o})/\partial q_{n})*\Delta q_{m}$$

Equation (4.16) is now in a form that we can represent using matrix equations. The advantage of equation (4.16) is that we can now solve for $\underline{q}_{n}$ explicitly.

In order to solve for $\underline{q}_{n}$, we first define the following relationships

$$D_{n} = \sum_{i=1}^{4}\sum_{j=1}^{3}\sum_{k=1}^{15} e_{ij}(k,\underline{q}^{o})*(\partial e_{ij}(k,\underline{q}^{o})/\partial q_{n}) \tag{4.17}$$

$$C_{n,m} = \sum_{i=1}^{4} \sum_{j=1}^{3} \sum_{k=1}^{15} (\partial e_{ij}(k,\underline{q}^{o})/\partial q_{n}) * (\partial e_{ij}(k,\underline{q}^{o})/\partial q_{m}) \quad (4.18)$$

Thus, in matrix form equation (4.16) may be written as

$$-\underline{D} = \underline{C}^{*}\ \underline{q} = \underline{C}^{*}(\underline{q} - \underline{q}^{o}) \quad (4.19)$$

Solving for $\underline{q}$, we have

$$\underline{q} = \underline{q}^{o} - \underline{C}^{-1} * \underline{D} \quad (4.20)$$

With $\underline{q} = \underline{q}(i+1)$ and $\underline{q}^{o} = \underline{q}(i)$, the Gauss-Newton algorithm for the Hexane Model is written as

$$\underline{q}(i+1) = \underline{q}(i) - \underline{C}^{-1} * \underline{D} \Big|_{\underline{q}=\underline{q}(i)} \quad (4.21)$$

Equation (4.21) is the specific algorithm used for estimating the parameters of the Hexane Model. The algorithm starts with an initial value of $\underline{q}(0)$. The partial derivatives could have been determined directly from the sensitivity functions. But, as was shown for the Steepest Descent method, it is very

tedious to derive the differential equations of the sensitivity functions. Therefore, the finite difference method is used to approximate the partial derivatives. We do note that equation (4.21) is similar to equation(3.12) except that equation (4.21) deals with discrete measurements instead of continuous measurements.

The method used for dealing with constraints is the same as that used for the Steepest Descent method. That is, when an estimate crosses over the boundary constraint, it is then replaced by that boundary constraint. The Gauss-Newton algorithm as implemented on the computer is presented in Figure 4.2.

Scalar Gauss-Newton Method. A simplified version of the Gauss-Newton algorithm was proposed by Dr. Quinn. (QUIN83) The simplification is recognized when we let the Gauss-Newton method update only one parameter at a time. If the Gauss-Newton algorithm updated only the parameter q_n, then the algorithm reduces to

$$q_n(i+1) = q_n(i) - \qquad (4.22)$$

$$\sum_{i=1}^{4}\sum_{j=1}^{3}\sum_{k=1}^{15} \left(e_{ij}(k,\underline{q}^o)*(\partial e_{ij}(\underline{q}^o)/\partial q_n\right)/$$

$$\left[\sum_{i=1}^{4}\sum_{j=1}^{3}\sum_{k=1}^{15} \left(\partial e_{ij}(k,\underline{q}^o)/\partial q_n\right)^2\right]$$

```
                    Gauss-Newton Algorithm

with the starting point q, evaluate ssq
DO WHILE (counter .LE. max_count)
find e(i,j,k) = (O(i,j,k) - y(i,j,k))/O(i,j,k)     for i=1 to 4,
                                                       j=1 to 3,
                                                       k=1 to 15

FOR n=1 to 7 DO
   with q_test(n) = 1.0001*q(n) and q_test(m) = q(m) for m≠n,
      find e_n(n,i,j,k)=(O(i,j,k) - y(i,j,k))/O(i,j,k)
      d_e(n,i,j,k) = (e_n(n,i,j,k) - e(i,j,k)/(1.0001*q(n))
ENDFOR n
FOR n = 1 to 7 DO
   FOR m=1 to 7 DO
      D(n) = 0.0
      C(n,m) = 0.0
      FOR i=1 to 4 DO
         FOR j=1 to 3 DO
            FOR k=1 to 15 DO
               C(n,m) = C(n,m) + d_e(n,i,j,k)*d_e(m,i,j,k)
               D(n) = D(n) + e(i,j,k)*d_e(n,i,j,k)
            ENDFOR k
         ENDFOR j
      ENDFOR i
   ENDFOR m
ENDFOR n
```

FIGURE 4.2 Gauss-Newton Algorithm

```
   evaluate q_new = q - C^-1 * D
   FOR i=1 to 7 DO
      IF (q_new(i) .LT. lowerbound_i) THEN
         q_new(i) = lowerbound_i
      ELSE IF (q_new(i) .LT. upperbound_i) THEN
         q_new(i) = upperbound_i
      ENDIF
   ENDFOR i
   evaluate ssq_test for q_new
   IF (ssq_test .LT. ssq) THEN
      q = q_new
      ssq = ssq_test
   ENDIF
   counter + counter + 1
ENDWHILE
The final estimate is q with a sum of s uares error of ssq
```

FIGURE 4.2 (continued)

This algorithm is in fact equivalent to the Gauss-Newton algorithm when all elements in the $\underline{C}$ matrix are zero except for the diagonal elements.

The advantage of the scalar form is two-fold. First, a large amount of computation is avoided since none of the cross-terms in the $\underline{C}$ matrix needs to be computed. In addition, no matrix inversion is required. Instead, we compute the inverse of $\underline{C}$ simply by inverting each diagonal element. The Scalar Gauss-Newton algorithm as implemented on the computer is presented in Figure 4.3.

Validation of the Computer Programs

Plots of both the data and the predicted values indicated absence of any major program logic errors or data input errors. As a check for further possible errors, the computer programs' results at each iteration were examined. These checks indicated that the algorithms correctly updated the estimates with feasible values that decreased the value of the error function.

Although the three optimization algorithms were working correctly, the values calculated in the error function still needed to be validated. This was done by verifying that the Hexane Model equations were implemented on the computer correctly.

Scalar Gauss-Newton Algorithm

```
evaluate ssq for the starting value q(0)
evaluate e(i,j,k) = (O(i,j,k) - y(i,j,k))/O(i,j,k)        for i=1,4
                                                                j=1,3
                                                                k=1,15

DO WHILE (counter .LE. max_count)
   FOR n=1 to 7 DO
      q_temporary = q(n)
      q(n) = 1.0001*q(n)
      evaluate ssq_new for q
      evaluate e_new(i,j,k) in the same manner as was done for
                                                          e(i,j,k)
      q(n) = q_temporary
      sum_num = 0.
      sum_den = 0.
      FOR i = 1 to 4 DO
         FOR j = 1 to 3 DO
            FOR k = 1 to 15 DO
               sum_num = sum_num + (e(i,j,k) - e_new(i,j,k))*
                                    e(i,j,k)/(.0001*q(n))
               sum_den = sum_den + (e(i,j,k) - e_new(i,j,k))^2/
                                    (.0001*q(n))^2
            ENDFOR k
         ENDFOR j
      ENDFOR i
```

FIGURE 4.3 Scalar Gauss-Newton Algorithm

```
      q_new(n) = sum_num/sum_den
      IF (q_new(n) .LT. lowerbound_n) THEN
        q_new(n) = lowerbound_n
      ELSE IF (q_new(n) .GT. upperbound_n) THEN
        q_new(n) = upperbound_n
      ENDIF
    ENDFOR n
    evaluate ssq_test for q_new
    IF (ssq_test .LT. ssq) THEN
      q = q_new
      ssq = ssq_test
    ENDIF
    counter = counter + 1
ENDWHILE
print out the results:  q and ssq
```

FIGURE 4.3 (continued)

To verify this, Dr. Quinn and Major Clewell both independently solved the Hexane Model equations on the computer. When their results agreed exactly with those in the optimization routines, it was concluded that the equations in fact were programmed into the optimization routines correctly.

Comparison of the Algorithms

Two types of comparisons were made for the three algorithms. In the first comparison, the number of additions and subtractions, multiplications, and divisions required by each of the algorithms were counted for each iteration. In addition, the number of times the IMSL subroutines DGEAR and LINV2F are called were counted. Recall that the subroutine DGEAR solves systems of stiff differential equations to determine the predicted values of the Hexane Model. The subroutine LINV2F computes the inverse of a matrix. The list of the number of function evaluations is given in Table 4.1.

TABLE 4.1 The number of function evaluations for each iteration of each algorithm

	# Additions/ # Subtractions	# Multiplications	# Divisions	DGEAR	LINV2F
Steepest Descent	14	21	7	8	---
Gauss-Newton	35,672	35,672	17,640	8	1
Scalar Gauss-Newton	3,794	3,787	1,267	8	---

We should note that the Steepest Descent computer program does not always pass through the same set of calculations at each iteration. The Steepest Descent algorithm calculates the gradient vector during the first iteration. However, it does not recompute the gradient vector at each iteration. If the current gradient vector fails to provide updates with a lower sum of squares value, even when the step size J has been decreased, then the gradient vector is recomputed in the next iteration. Table 4.1 lists the number of function evaluations for the case of the Steepest Descent algorithm computing the gradient vector. If the Steepest Descent algorithm did not evaluate the gradient this iteration, then there would be no divisions and only one call to DGEAR. In addition, the number of subtractions and the number of multiplications each equals seven.

The comparison in Table 4.1 shows that the Gauss-Newton algorithm has many more function evaluations than both the Steepest Descent algorithm and the Scalar Gauss-Newton algorithm. On a smaller scale, the Scalar Gauss-Newton algorithm has more function evaluations than the Steepest Descent algorithm. The optimization strategy to be employed combines the Steepest Descent algorithm and only one of the Gauss-Newton algorithms. Thus, of primary concern is the comparison between the two Gauss-Newton algorithms since only one of them will be used. A second comparison was made to

decide if the computational expense of the Gauss-Newton algorithm over the Scalar Gauss-Newton algorithm is worth the convergence speed it provides.

In the second comparison, the algorithms' performances were determined. Each algorithm was timed for speed in executing a given number of iterations. Also, the sum of squares error was tabulated. The results are shown in Tables 4.2 and 4.3.

TABLE 4.2 Time (secs)

# of iterations	Steepest Descent	Gauss-Newton	Scalar Gauss-Newton
1	35.106	193.132	55.786
2	38.479	388.954	101.231
3	41.303	580.838	146.347
5	43.686	967.780	236.901
10	44.909	1912.042	459.229

Results for the two Gauss-Newton methods were unexpected. The Scalar Gauss-Newton algorithm seemed to achieve slightly smaller sum of squares error values than the full Gauss-Newton algorithm. The opposite was expected. In addition, the full

Gauss-Newton method took much more time to execute each iteration. This seemingly poorer performance of the full Gauss-Newton algorithm perhaps can be attributed to the numerical errors that may be introduced with the greater number of computations it performs. Based on the results, the full Gauss-Newton algorithm was excluded from any further optimization runs.

TABLE 4.3 Sum of squares error

# of iterations	Steepest Descent	Gauss-Newton	Scalar Gauss-Newton
1	32.171	26.772	25.361
2	32.171	26.035	24.807
3	32.171	25.663	24.513
5	30 659	24.970	24.225
10	28.070	24.574	24.022

One further comment should be made about the algorithms. Little effort was made to reduce the calculations involved in each algorithm to the minimum. After the results shown in Tables 4.2 and 4.3 were gathered, the author has noted that the amount of function evaluations in the full Gauss-Newton method can be reduced. However, in the interest of time, the reduced amount of function evaluations could not be implemented.

V. Estimation of the Parameters

Once the optimization routines were implemented on the computer, the estimation process was initiated. This process was iterative in that estimation results were frequently passed to AFAMRL after which they returned with further modifications to the model. For parameter estimation of the Hexane Model, preliminary results were first examined by Dr. Anderson and Major Clewell to ensure that they made physical sense. Any discrepancies that the researchers noted were then corrected. Next, each of the algorithms' performance was studied to see which step sizes appeared to be the most efficient. Third, several starting values were selected as part of a strategy for seeking the global minimum. Finally, the estimation results were examined by AFAMRL before acceptance.

Preliminary Results for Model Validation

Some computer runs were initially made using starting values recommended by Dr. Anderson and Major Clewell. These routines were sent to AFAMRL to be critiqued. AFAMRL's

recommendations were then incorporated into the routines before a large amount of effort was expended into estimating the parameters. As it turned out, the data plots proved invaluable since AFAMRL could judge for themselves the performance of the optimization routines. The plots also allowed AFAMRL to quickly detect some discrepancies between the model and the data. In light of these discrepancies, Dr. Anderson changed the following parameters in the Hexane Model to

PB = .8
PF = 200.
PR = 11.5
PS = 3.62

These changes provided a better fit between the data and the predicted value of concentration levels of hexane in the blood.

Step Sizes for Efficient Algorithm Implementation

In the Steepest Descent algorithm, the sum of squares error was examined for various values of the step size J. The results are shown in Table 5.1. It appears from Table 5.1 that for the Hexane Model, the Steepest Descent method works most efficiently with the step size J = .001. This result, however, may not apply for different starting values, different

error functions, or different pharmacokinetic models.

TABLE 5.1 Sum of Squares Error for the Steepest Descent Algorithm

Number of Iterations	Step Size				
	.00001	.0001	.001	.01	.1
1	37.306	36.449	34.703	37.416	37.416
2	37.199	35.735	34.703	34.703	37.416
5	36.897	34.649	32.525	33.607	34.703

Next, the sum of squares error was examined in the Hexane Model for the various normalized step sizes $\Delta q_n/q_n$ used in the Scalar Gauss-Newton method. Recall that Δq_n was used as part of the finite difference method for approximating the derivatives. The results are shown in Table 5.2.

TABLE 5.2 Sum of Squares Error for the Scalar Gauss-Newton Algorithm

Number of Iterations	Normalized Step Size $\Delta q_n/q_n$				
	.00001	.0001	.001	.01	.1
1	29.855	29.909	29.721	29.804	29.897
2	29.033	29.223	29.156	29.286	29.383
5	28.663	28.617	28.607	28.671	28.736

The normalized step size $\Delta q_n/q_n = .00001$ should provide the best approximation to the derivatives. However, Table 5.2 shows that the value $\Delta q_n/q_n = .001$ might be used without degrading performance. Again, we note that these results may vary with the choice of starting values, error function, or pharmacokinetic model.

Selecting the Initial Values

After obtaining these preliminary results about the Hexane Model and the optimization algorithms, a procedure to obtain the global optimum was started. First, an initial set of starting values were selected. In this case, the selected values were the upper and lower bounds of the unknown parameters. This gives a total of 128 possible starting points. The option of using a larger number of starting points was considered, but it was noted that such an increase was too large to handle in the time allocated for this research. For example, if we had selected 3 values instead of 2 values for each of the unknown parameters, then a total of 2,187 starting points would need to be evaluated. However, it was concluded that examining 2,187 possible starting points was too large a task for this thesis effort. Fortunately, AFAMRL agreed that the 128 starting points would be sufficient to explore the possibilities. Hence, only the 128 possible starting points were selected for

further analysis.

For each of the 128 possible starting points, the sum of squares error was computed. The results were then scanned so that points with a sum of squares error below 45 could be selected as starting points. The other starting points were discard. The 12 points with a sum of squares error below 45 are shown in Table 5.3.

TABLE 5.3 Selected Starting Values

#	KFO	VMAX2	KM2	VMAX3	KM3	KM2I	K	SSQ
1	2.4	.2	.1	5.0	10.0	1.0	.6	36.5
2	2.4	.2	.1	5.0	10.0	1000.0	.6	36.3
3	2.4	.2	10.0	5.0	10.0	1.0	.1	43.9
4	2.4	2.0	10.0	5.0	10.0	1.0	.1	39.3
5	2.4	2.0	10.0	5.0	10.0	1.0	.6	41.8
6	2.4	2.0	10.0	5.0	10.0	1000.0	.6	41.0
7	4.4	.2	.1	5.0	10.0	1.0	.6	35.9
8	4.4	.2	.1	5.0	10.0	1000.0	.6	36.4
9	4.4	.2	10.0	5.0	10.0	1.0	.1	43.6
10	4.4	2.0	10.0	5.0	10.0	1.0	.1	38.8
11	4.4	2.0	10.0	5.0	10.0	1.0	.6	41.3
12	4.4	2.0	10.0	5.0	10.0	1000.0	.6	41.0

In addition to the 12 starting points presented in Table 5.3, AFAMRL provided starting values based upon what they felt would be the best estimate of the parameters. Their starting values are shown in Table 5.4. Altogether, 13 starting points were used by the optimization algorithms.

TABLE 5.4 Starting Values Recommended by AFAMRL

KFO	VMAX2	KM2	VMAX3	KM3	KM2I	K	SSQ
3.4,	.35	1.0	2.6	3.0	100.0	.2	37.416

Estimation Results

Each of the 12 points in Table 5.3 were first used as starting values for the Steepest Descent algorithm. The Steepest Descent algorithm then updates the initial values 3 times. These few iterations are intended to bring the initial values closer to a local minimum. The resulting estimates are then used for further optimization with the Scalar Gauss-Newton method. Since the initial values are relatively close to a local minimum after passing through the Steepest Descent algorithm, the

Gauss-Newton algorithm should be effective in finding results that give a reduction in the sum of squares error.

With the estimates from the Steepest Descent method, the Scalar Gauss-Newton method then proceeds through 15 more iterations. For the 12 starting points presented in Table 5.3, their final estimates are shown in Table 5.5.

TABLE 5.5 Final results from the starting values in Table 5.3

#	KFO	VMAX2	KM2	VMAX3	KM3	KM2I	K	SSQ
1	2.594	.299	.216	4.140	9.932	1.213	.310	30.412
2	3.618	.278	.163	4.816	7.243	174.948	.367	30.503
3	2.585	1.986	2.758	3.876	8.631	1.279	.295	30.165
4	4.400	1.920	7.424	4.490	9.406	1.011	.162	33.261
5	2.619	2.000	2.816	4.326	9.627	1.324	.295	30.171
6	4.400	2.000	3.875	5.000	7.300	153.194	.322	29.652
7	4.400	.400	.183	4.945	10.000	1.200	.444	31.959
8	4.092	.328	.170	5.000	8.371	440.941	.431	30.975
9	2.948	2.000	3.550	4.423	9.739	1.421	.277	30.312
10	3.231	2.000	3.901	3.976	8.159	1.521	.270	30.305
11	3.161	2.000	2.873	4.631	9.643	1.753	.299	30.117
12	4.4	2.000	3.760	3.890	6.591	1000.000	.315	29.518

In addition to the 12 starting points of Table 5.3, the starting values provided by AFAMRL underwent 3 iterations of the Steepest Descent algorithm and then 15 iterations of the Scalar Gauss-Newton algorithm. The results for this case are shown in Table 5.6.

TABLE 5.6 Results from the starting values provided provided by AFAMRL in Table 5.4

KFO	VVMAX2	KM2	VMAX3	KM3	KM2I	K	SSQ
2.4	.4025	.5317	2.8177	2.5132	1000.0	.2931	28.428

Of the 13 results presented in Tables 5.5 and 5.6, the starting point provided by AFAMRL showed the lowest value in its sum of squares error. The results shown in Table 5.6 were thus forwarded to AFAMRL for approval. The major factor influencing AFAMRL's decision to accept the estimate was not necessarily the low value for the sum of squares error. Rather, the plots provided a clear picture of the performance of the estimates to AFAMRL. The estimates were thus accepted since the plots showed that for the Hexane Model, the predicted values match the data closely in many of the plots. The plots are shown in Figure 5.1.

A final comment should be made about the results. With the many updates that AFAMRL made to the model, the final error function in the algorithms did not exactly represent the Hexane Model used in this thesis. However, as it turns out, the error function still measured the agreement between the predicted values and the experimental data. The estimates, although perhaps not global, served their purpose by indicating to the scientists the underlying processes involved with the hexane in the mammal. The results met AFAMRL's approval.

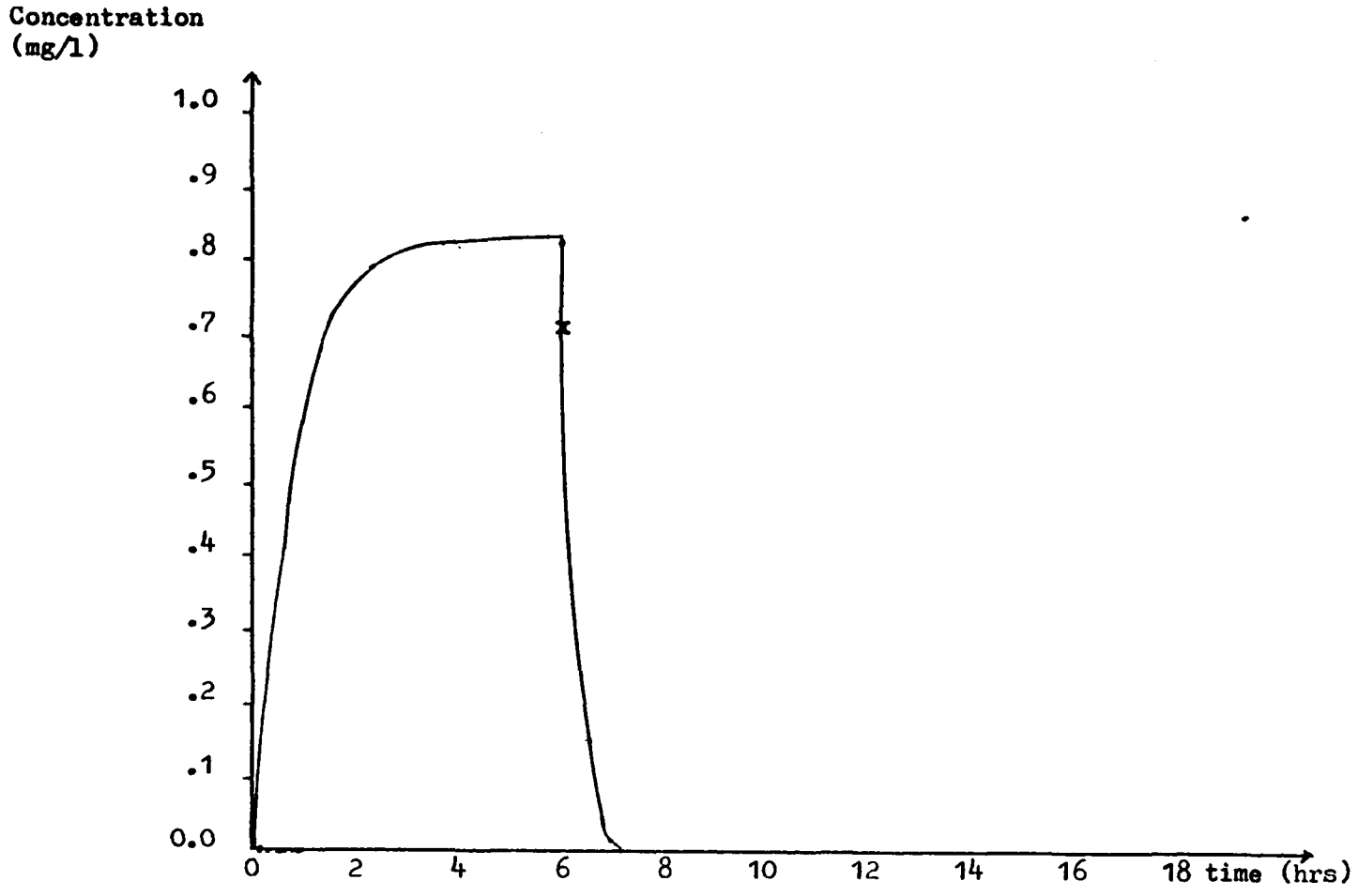

FIGURE 5.1(a) Concentration of methyl-n-butylketone in body water: Run #1

Note: (solid line) - predicted values
x - experimental observations

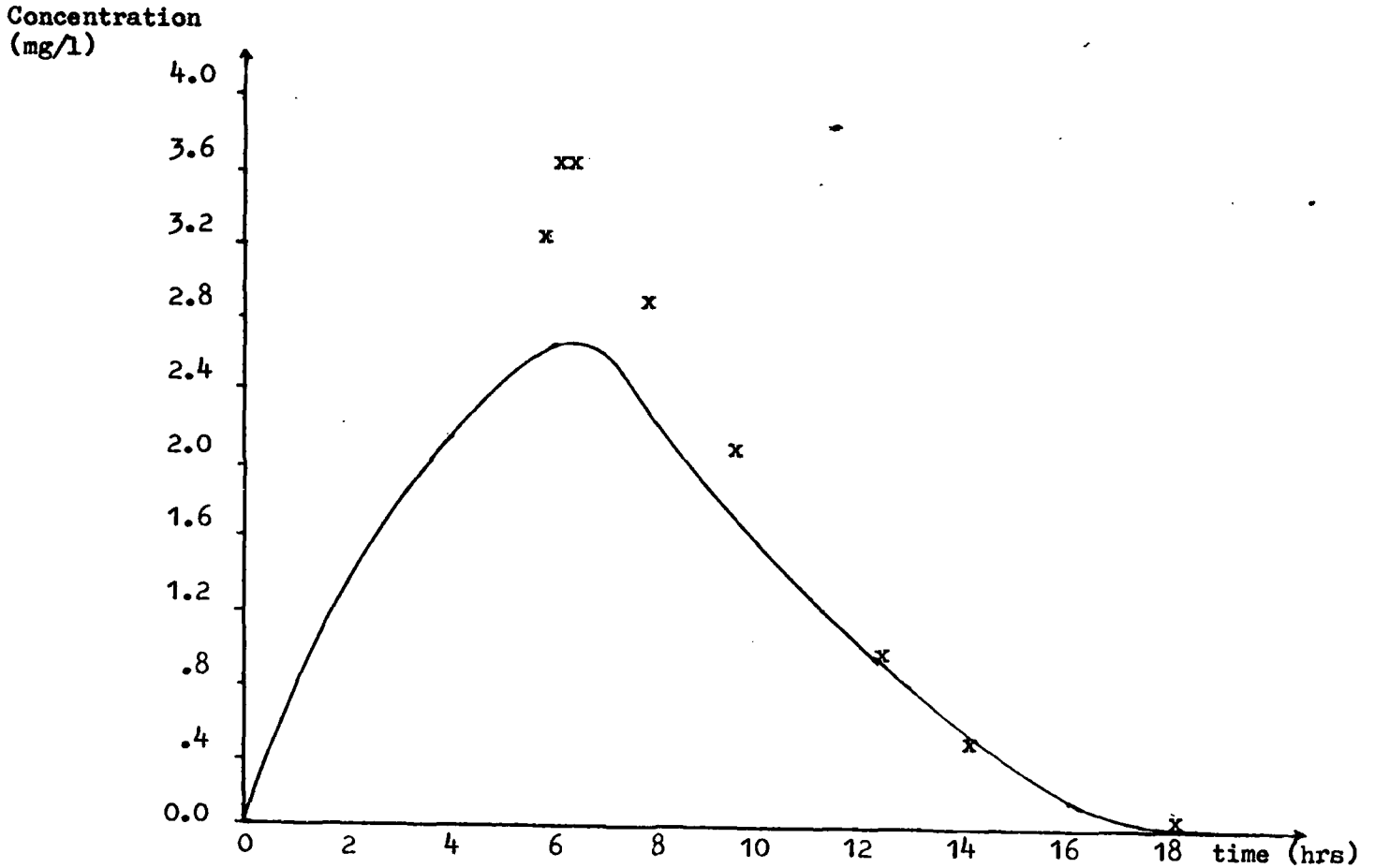

FIGURE 5.1(b) Concentration of 2,5-hexanedione in body water: Run #1

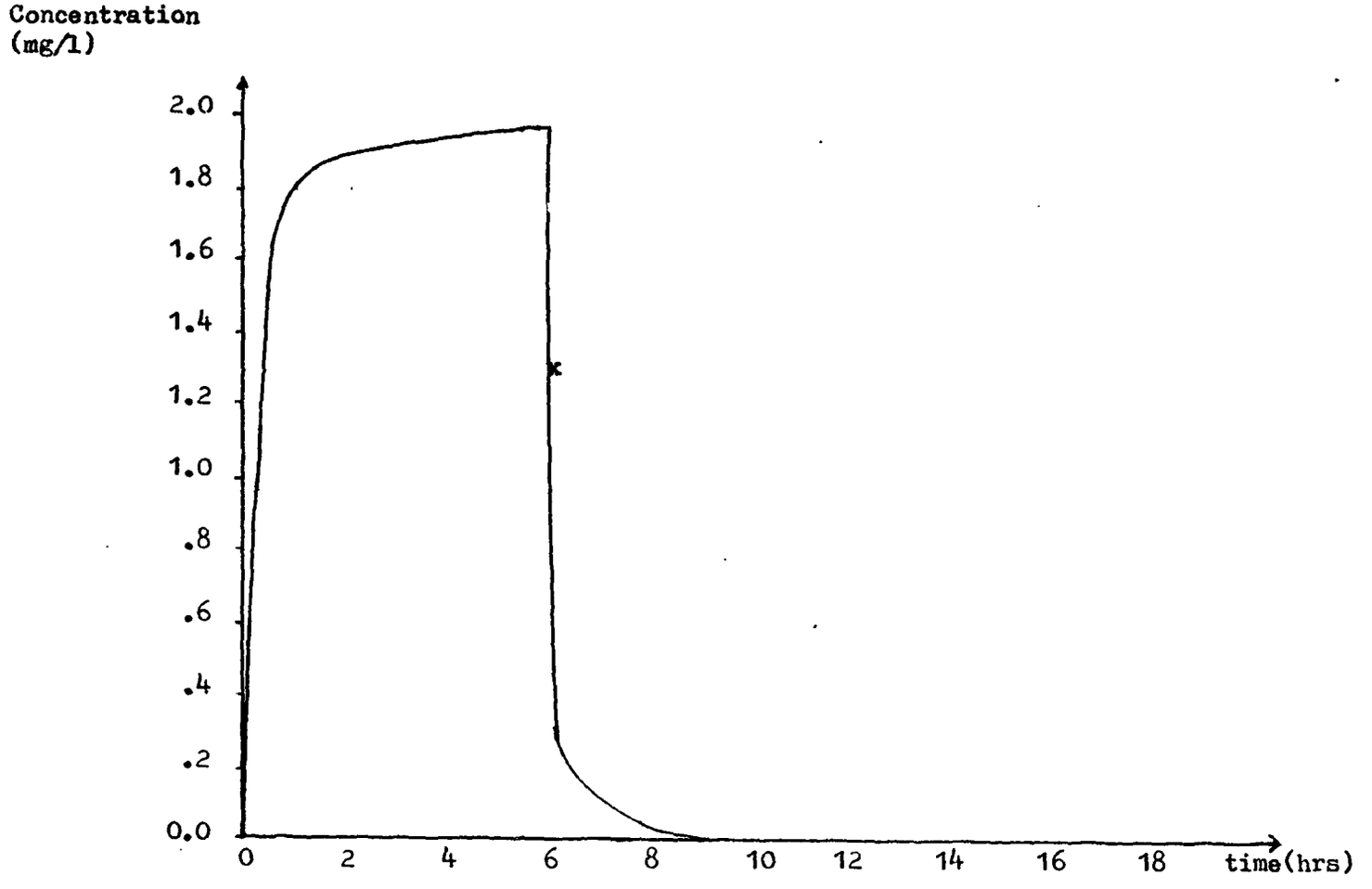

FIGURE 5.1(c) Concentration of hexane in the blood: Run #1

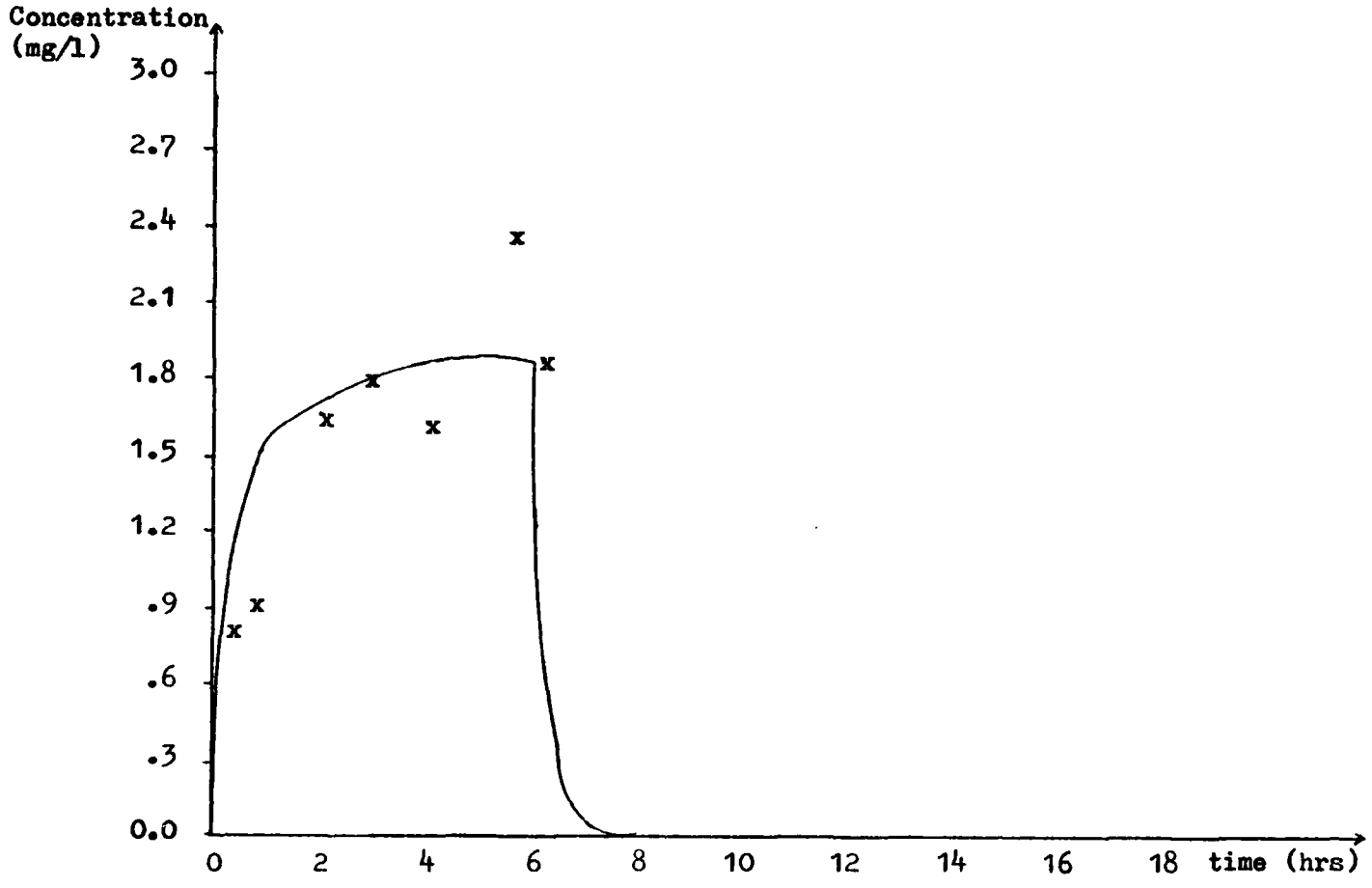

FIGURE 5.1(d) Concentration of methyl-n-butylketone in body water: Run #2

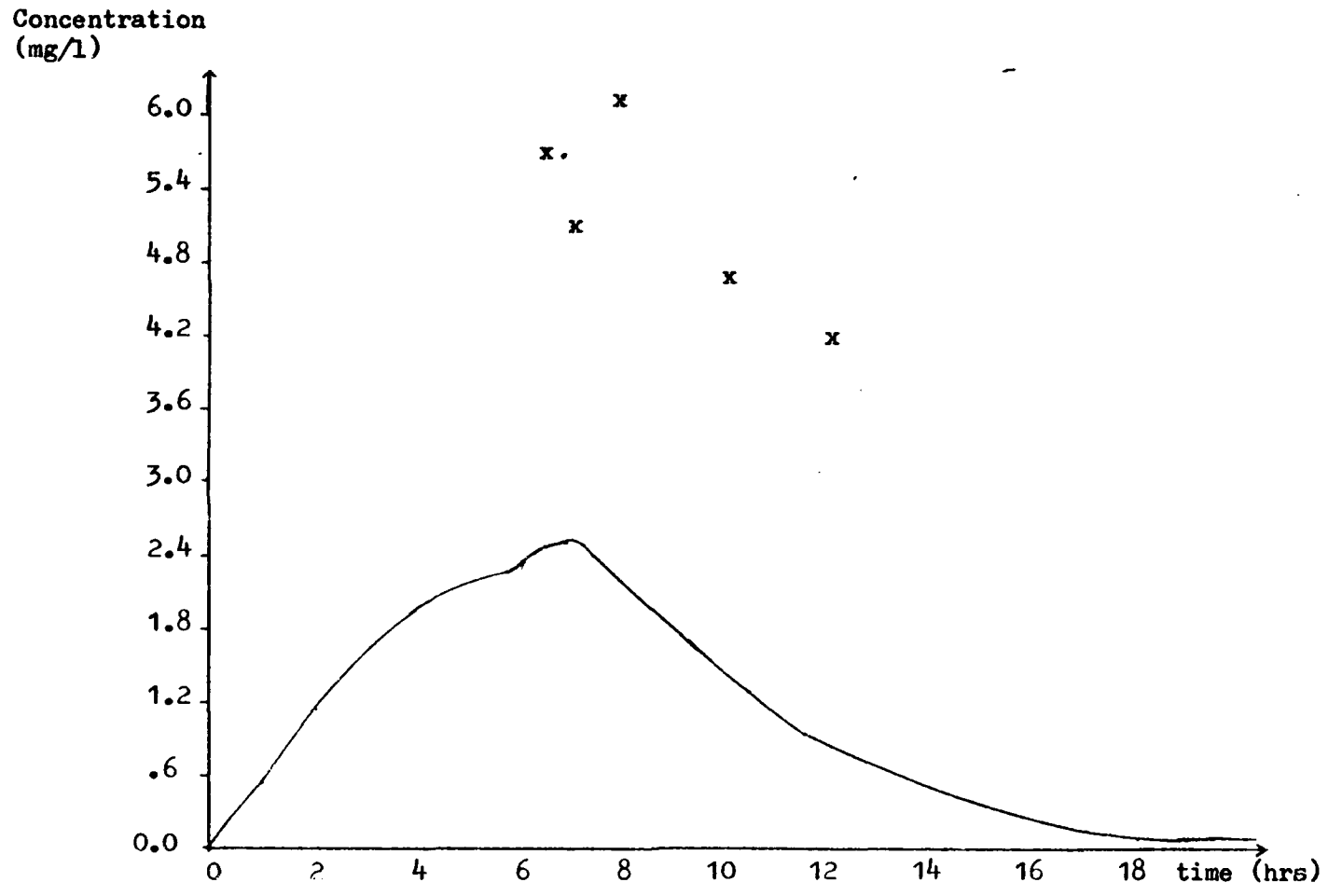

FIGURE 5.1(e) Concentration of 2,5-hexanedione in body water: Run #2

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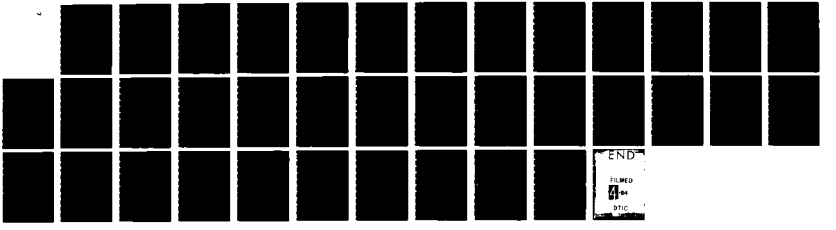

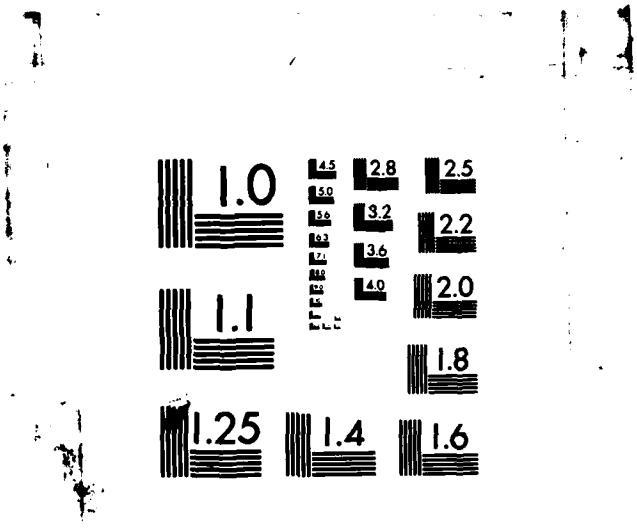

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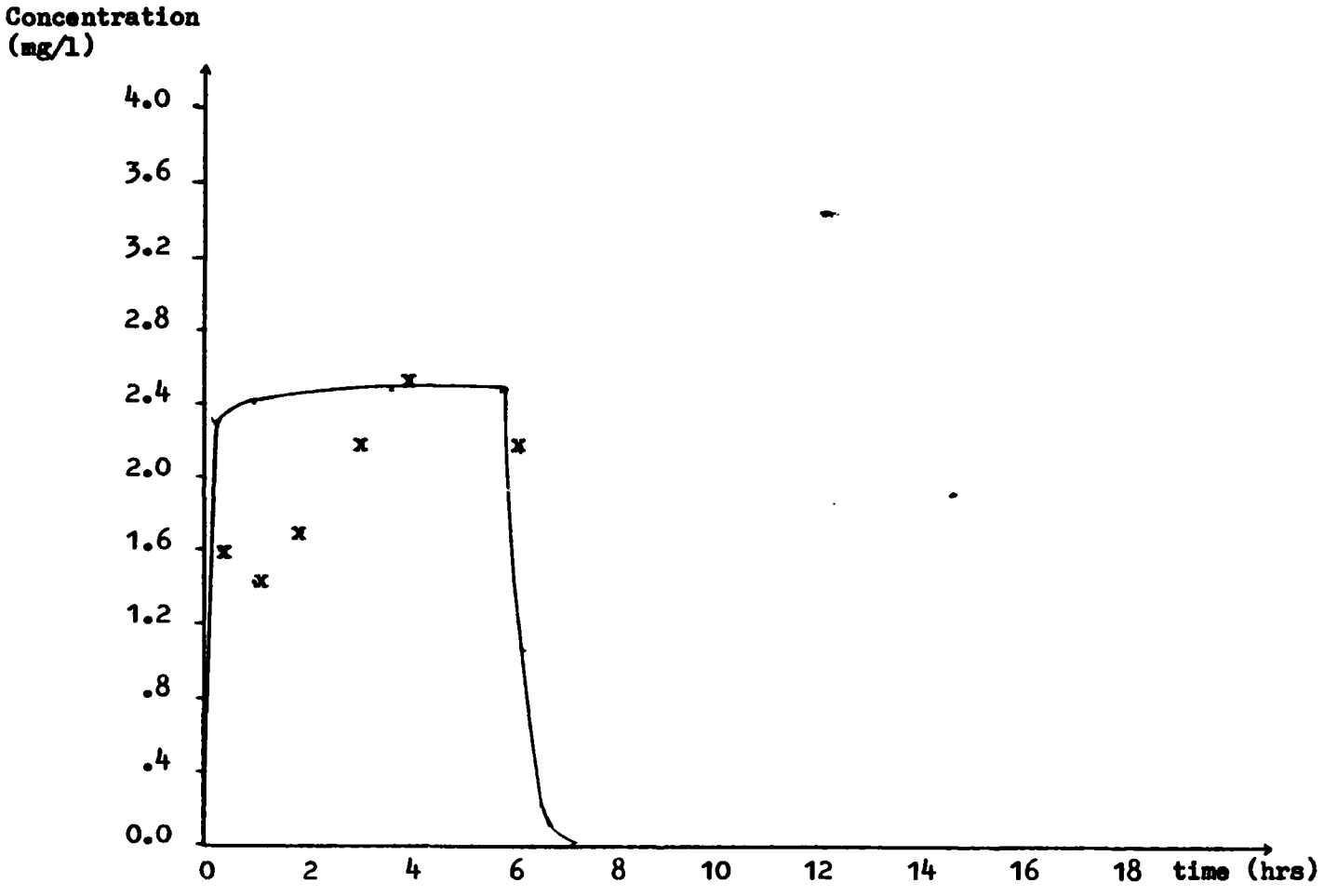

FIGURE 5.1(f) Concentration of hexane in the blood: Run #2

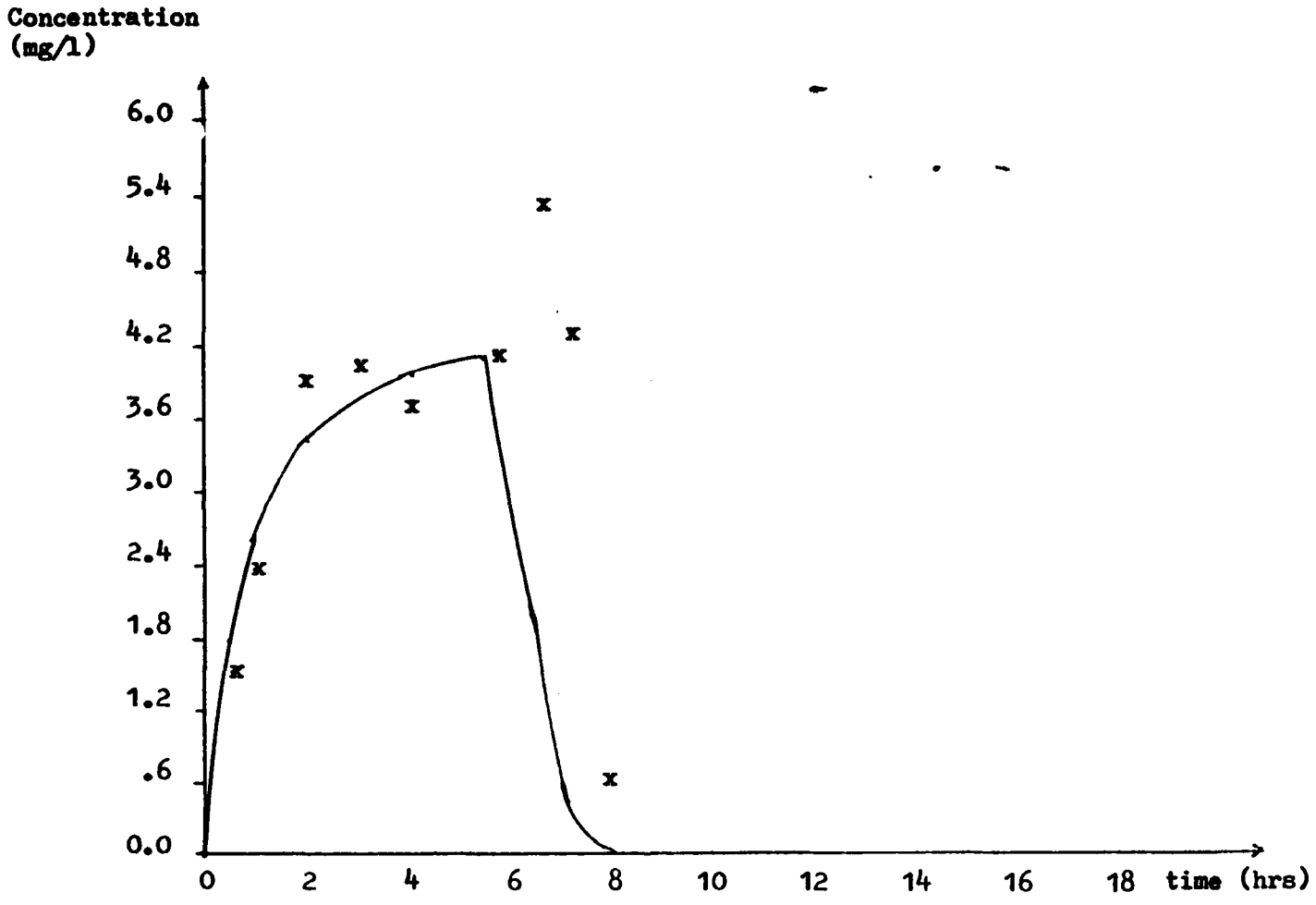

FIGURE 5.1(g) Concentration of methyl-n-butylketone in body water: Run #3

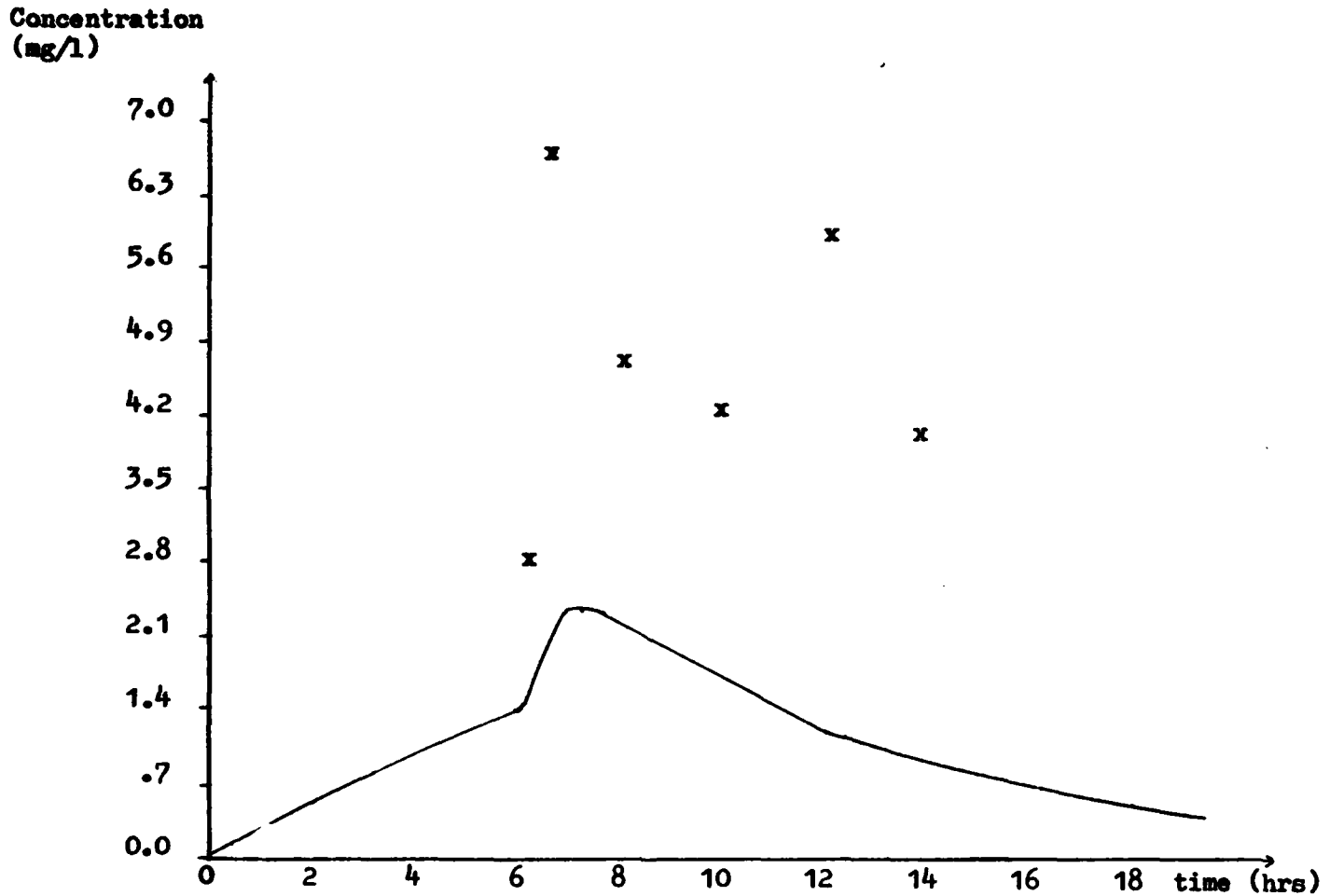

FIGURE 5.1(h) Concentration of 2,5-hexanedione in body water: Run #3

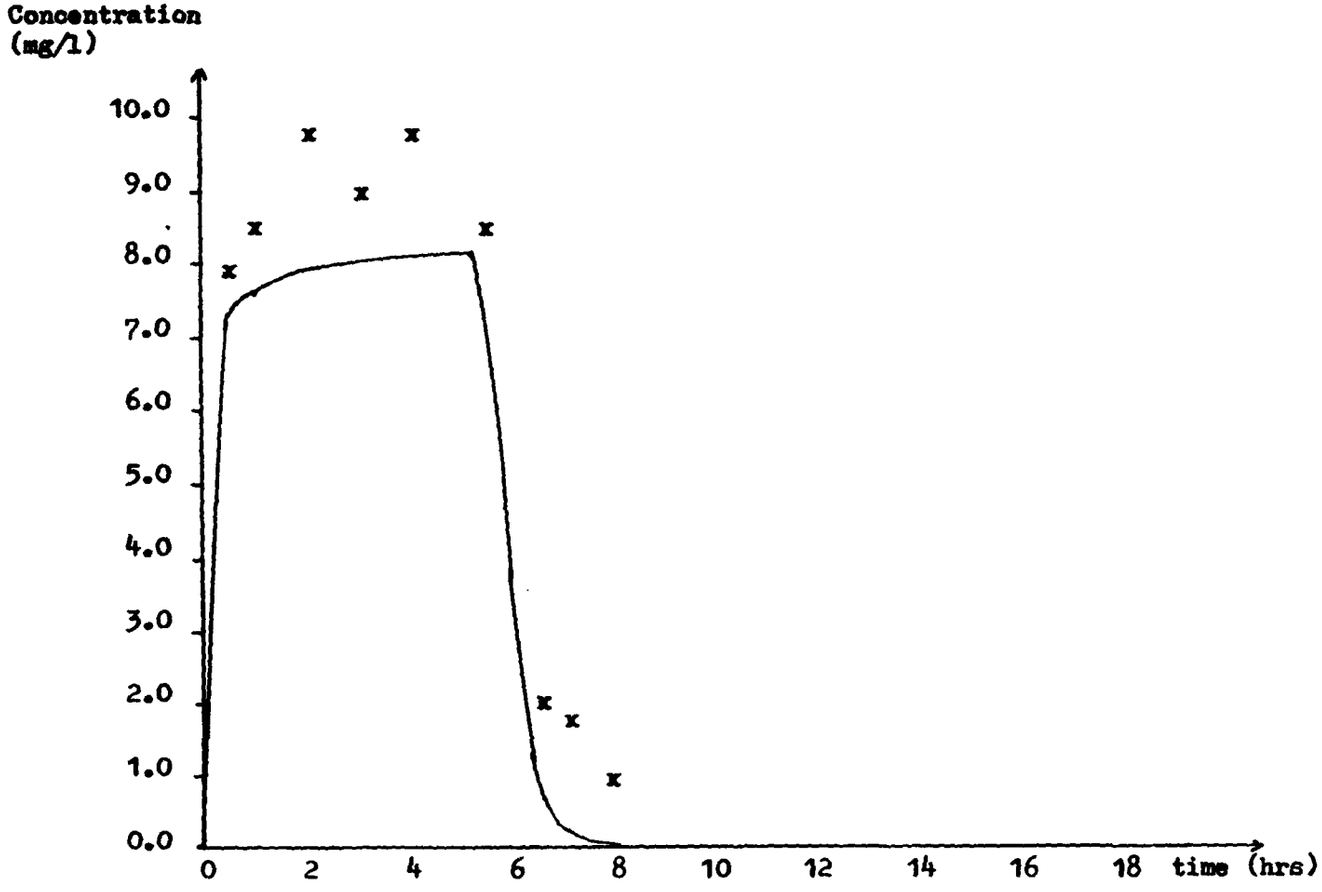

FIGURE 5.1(i) Concentration of hexane in the blood: Run #3

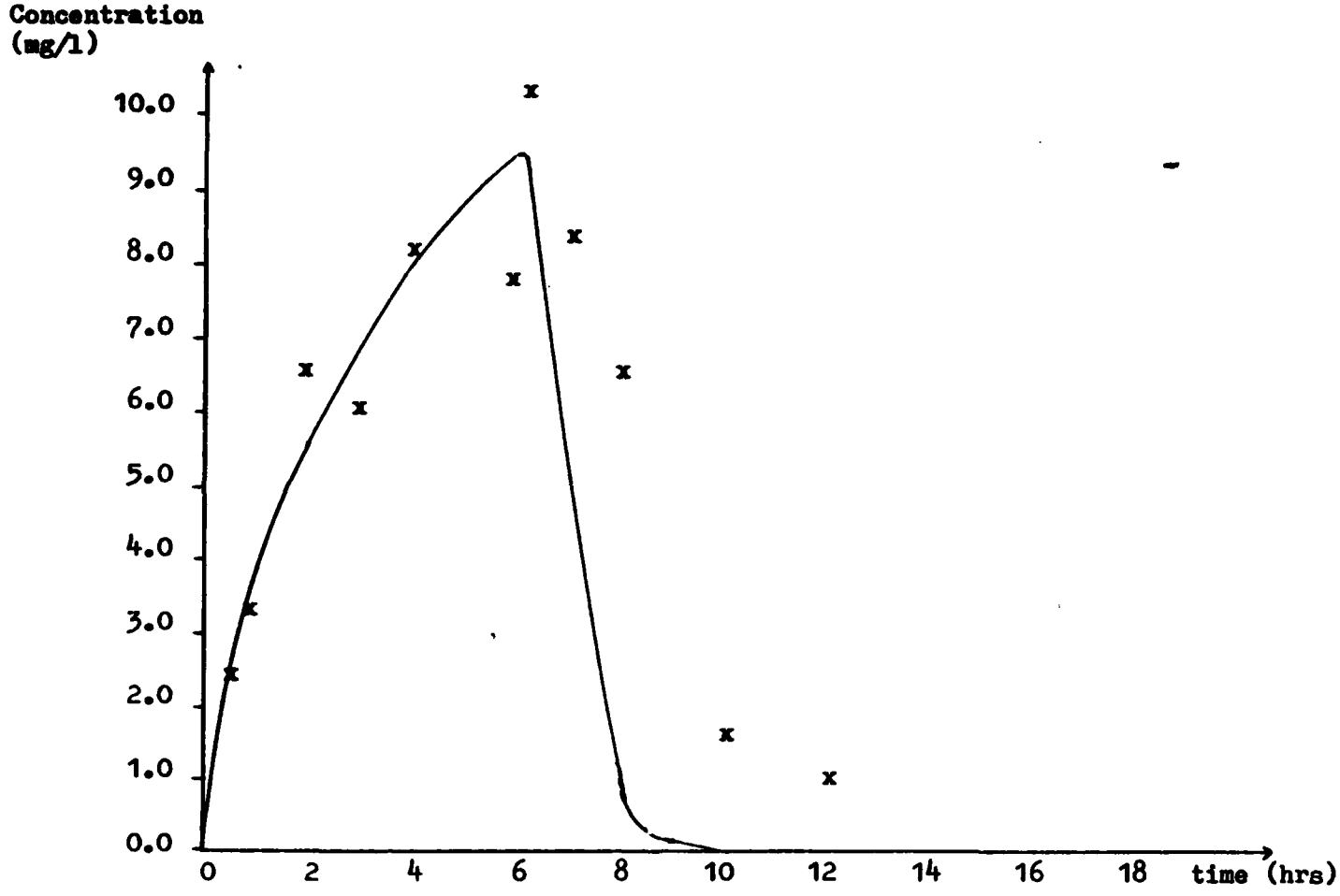

FIGURE 5.1(j) Concentration of methyl-n-butylketone in body water: Run #4

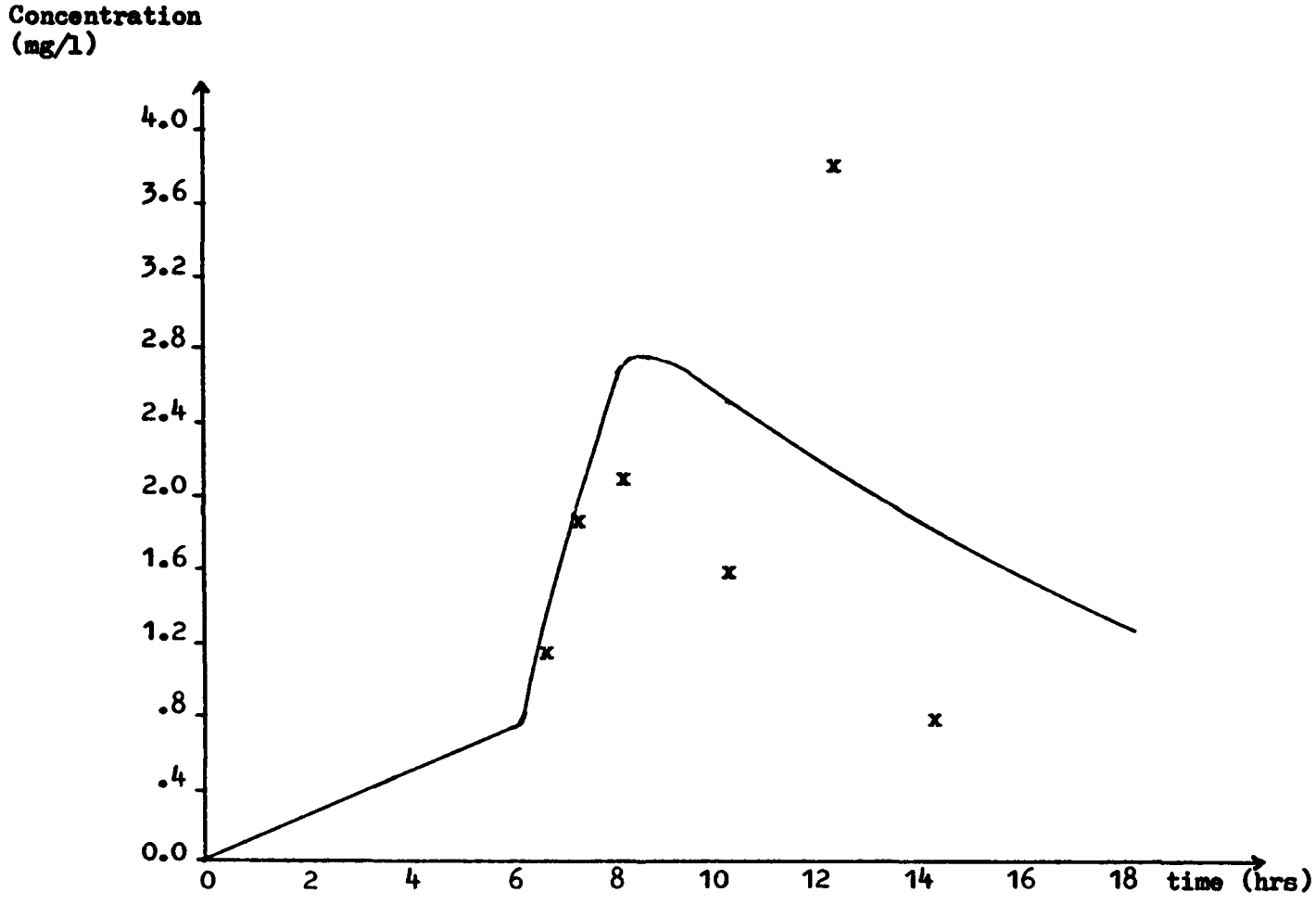

FIGURE 5.1(k) Concentration of 2,5-hexanedione in body water: Run #4

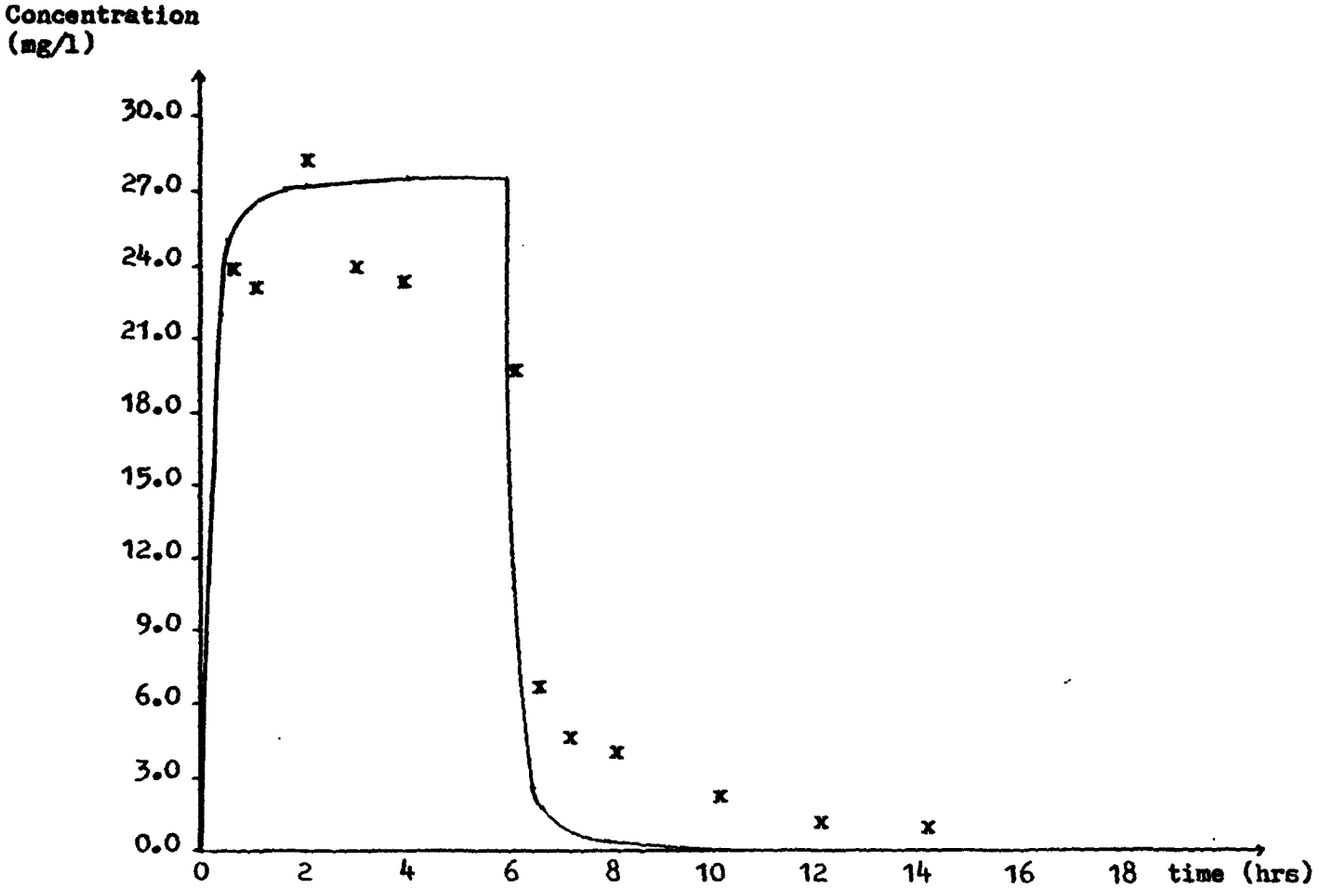

FIGURE 5.1(1) Concentration of hexane in the blood: Run #4

VI. Sensitivity Analysis

For the estimates of the unknown parameters obtained in Chapter V, a sensitivity analysis was conducted. The analysis was intended to aid the researchers at AFAMRL in determining which set of the estimated parameters had a large impact on the error function. One of the purposes for determining this is to help AFAMRL in designing future experiments. By understanding which parameters affected the error function heavily, the researchers could then experiment in an attempt to estimate precisely the more influential parameters. In the meantime, the least influential parameters may be eliminated from further estimation.

In this chapter, a post-experimental sensitivity analysis was conducted first. This type of analysis is typically conducted after the experimentation and parameter estimation. From it come clues about how a change in the estimates would affect the error function. In essence, post-experimental sensitivity analysis indicates the degree to which each parameter is estimated precisely.

The second type of analysis involves the examination of sensitivity functions. This type of analysis may be used before experimentation. For this thesis, the analysis of sensitivity functions was relatively brief. The intent of this analysis was to introduce the researchers to the possibilities of experimental design of dynamical systems. Although brief, the discussion of this type of analysis should provide the researchers a useful starting point to designing experiments with sensitivity functions.

Post-Experimental Sensitivity Analysis

For post-experimental sensitivity analysis, the approach used is similar to that recommended by Lehman and Stark. To begin with, each of the values were evaluated at a factor of $\pm$ .00001 away from their estimates. The sum of squares error for each of these perturbed values is shown in Table 6.1. Next, the factor was increased by a multiple of 3. Thus, a second set of perturbed values had their sum of squares error computed at a factor of $\pm$ .00003 away from their estimates. This process of increasing the perturbation factor by a multiple of 3 was continued several times. For each perturbed value, the sum of squares error was computed. The results are displayed in Table 6.1.

TABLE 6.1(a) Sensitivity Analysis for KFO

Factor Δ	KFO*(1 - Δ)	SSQ	KFO*(1 + Δ)	SSQ
.00001	2.399976	28.430	2.400024	28.430
.00003	2.399928	28.430	2.400072	28.430
.00009	2.399784	28.430	2.400216	28.430
.00027	2.399352	28.430	2.400648	28.431
.00081	2.398056	28.430	2.401944	28.430
.00243	2.394168	28.429	2.405832	28.431
.00729	2.382504	28.427	2.417496	28.434
.02187	2.347512	28.411	2.452488	28.443
.06561	2.242536	28.411	2.557464	28.479
.19683	1.927608	28.455	2.872392	28.670
.59049	.982824	29.092	3.817176	30.114

TABLE 6.1(b) Sensitivity Analysis for VMAX2

Factor Δ	VMAX2*(1 - Δ)	SSQ	VMAX2*(1 + Δ)	SSQ
.00001	.4025256	28.430	.4025336	28.430
.00003	.4025175	28.430	.4025417	28.430
.00009	.4024934	28.430	.4025658	28.430
.00027	.4024209	28.430	.4026383	28.431
.00081	.4022036	28.430	.4028556	28.431
.00243	.4015515	28.429	.4035078	28.432
.00729	.3995952	28.427	.4054641	28.434
.02187	.3937263	28.425	.4113329	28.447
.06561	.3761196	28.451	.4289396	28.513
.19683	.3232998	28.835	.4817595	28.964
.59049	.1648399	33.402	.6402193	32.181

TABLE 6.1(c) Sensitivity Analysis for KM2

Factor Δ	KM2*(1 - Δ)	SSQ	KM2*(1+ Δ)	SSQ
.00001	.5317015	28.430	.5317121	28.430
.00003	.5316908	28.430	.5317227	28.430
.00009	.5316589	28.430	.5317546	28.430
.00027	.5315632	28.430	.5318503	28.430
.00081	.5312761	28.430	.5321375	28.430
.00243	.5304147	28.430	.5329988	28.430
.00729	.5278306	28.431	.5355829	28.430
.02187	.5200783	28.433	.5433352	28.432
.06561	.4968215	28.451	.5665921	28.447
.19683	.4270509	28.652	.6363626	28.564
.59049	.2177392	32.441	.8456743	29.266

TABLE 6.1(d) Sensitivity Analysis for VMAX3

Factor Δ	VMAX3*(1 - Δ)	SSQ	VMAX3*(1 + Δ)	SSQ
.00001	2.817675	28.430	2.817732	28.430
.00003	2.817619	28.430	2.817789	28.430
.00009	2.816943	28.430	2.818465	28.431
.00027	2.816943	28.430	2.818465	28.430
.00081	2.815422	28.430	2.819986	28.431
.00243	2.810857	28.429	2.824551	28.433
.00729	2.797163	28.432	2.838245	28.443
.02187	2.756081	28.479	2.879327	28.507
.06561	2.632835	29.047	3.002574	28.957
.19683	2.263095	38.166	3.372313	31.509
.59049	1.153878	1199.806	4.481530	39.159

TABLE 6.1(e) Sensitivity Analysis for KM3

Factor Δ	KM3*(1 - Δ)	SSQ	KM3*(1 + Δ)	SSQ
.00001	2.513165	28.430	2.513216	28.430
.00003	2.513115	28.430	2.513266	28.430
.00009	2.512964	28.430	2.513417	28.430
.00027	2.512512	28.430	2.513869	28.430
.00081	2.511155	28.430	2.515226	28.430
.00243	2.507083	28.430	2.519297	28.430
.00729	2.494869	28.430	2.531512	28.431
.02187	2.458226	28.436	2.568154	28.439
.06561	2.348300	28.495	2.678081	28.500
.19683	2.018519	29.095	3.007862	28.992
.59049	1.029177	36.640	3.997204	32.695

TABLE 6.1(f) Sensitivity Analysis for KM2I

Factor Δ	KM2I*(1 - Δ)	SSQ	KM2I*(1 + Δ)	SSQ
.00001	999.99	28.430	1000.01	28.430
.00003	999.97	28.430	1000.03	28.430
.00009	999.91	28.430	1000.09	28.430
.00027	999.73	28.430	1000.27	28.430
.00081	999.19	28.430	1000.81	28.430
.00243	997.57	28.430	1002.43	28.430
.00729	992.71	28.430	1007.29	28.430
.02187	978.13	29.430	1021.87	28.430
.06561	934.39	28.430	1065.61	28.430
.19683	803.17	28.431	1196.83	28.430
.59049	409.51	28.436	1590.49	28.429

TABLE 6.1(g) Sensitivity Analysis for K

Factor Δ	$K^*(1 - \Delta)$	SSQ	$K^*(1 + \Delta)$	SSQ
.00001	.2930817	28.430	.2930875	28.430
.00003	.2930758	28.430	.2930934	28.430
.00009	.2930582	28.430	.2931110	28.430
.00027	.2930055	28.430	.2931637	28.430
.00081	.2928472	28.430	.2933220	28.430
.00243	.2923724	28.430	.2937970	28.430
.00729	.2909480	28.432	.2952212	28.432
.02187	.2866748	28.444	.2994944	28.441
.06561	.2738553	28.560	.3123139	28.523
.19683	.2353968	30.061	.3507724	29.074
.59049	.1200211	84.209	.4661481	31.438

From Table 6.1, it appears that, in general, very small changes in all of the parameters do not affect the error function. The parameter VMAX3, however, affects the error function much more than all other parameters at most of the perturbation values. At the perturbation factor of .59049, VMAX3 has the largest sum of squares error of 1199.806. Comparing the other error values in VMAX3 with that of the other parameters, we conclude that the estimate for VMAX3 must be known as closely as possible in order that the model closely fit the data.

The parameter KM2I, on the other hand, does not appear to affect the error function at all. This implies that the estimate for KM2I may not need to be precise at all. AFAMRL may consider leaving KM2I as a known constant in future experiments since its value may have little effect on the final estimates.

Sensitivity Functions for Experimental Design

The use of sensitivity functions for experimental design may be valuable for AFAMRL. The researchers are concerned about how they might conduct future experiments with the Hexane Model. In pharmacokinetic applications, it appears that the number of data points from an experiment is not necessarily large.

In addition, the length of the experiment may be constrained by time limits. With such limitations on the experiment, a careful plan for experimentation becomes important. Hence, the analysis of sensitivity functions before experimentation is appropriate for pharmacokinetic applications.

The analysis of sensitivity functions covered in this section is relatively brief. The topic itself can be involved enough to warrant a thesis effort solely devoted to experimental design topics for dynamical systems. The intent of this section is to introduce AFAMRL and other readers to the applications of sensitivity functions. To do this, we first consider the problem of weighting the sensitivity functions. This problem has not been resolved in this thesis effort, but it can be the starting point of another thesis. Next, some sensitivity functions are considered for the experiment which has already been conducted on the Hexane Model. By doing this, we can compare what we already know from the post-experimental sensitivity analysis with the results of the sensitivity functions. Next, a small example of experimental design is presented. Finally, a brief comment is made about optimal input design.

The Proper Weighting of Sensitivity Functions. Chapter III presented some concepts about using sensitivity functions for experimental design. However, it is still not clear from the

literature exactly how we might go about using these sensitivity functions. For example, Lehman and Stark suggest plotting the sensitivity functions

$$\partial y_j / \partial q_n$$

in order to get a feeling for which parameters q_n have the most influence on each of the measurements y_j. Lehman and Stark then recommend that the sensitivity functions be normalized by the nominal parameter q_n. This way, the plots of the magnitudes of the sensitivity functions can be directly compared with each other. Then the plots with the larger magnitudes identify the parameters that are likely to have a large impact on the error function. The plots also show the points in time when an experimental observation is likely to have a large effect in estimating the parameter under consideration. (LEHM81: 114-117)

As reported in Chapter III, Beck and Arnold recommend that for single response cases, the sensitivity functions be normalized in the same manner as that recommended by Lehman and Stark. However, for the multiple response case, Beck and Arnold add that the sensitivity function be further normalized by the standard deviation of the measuring instruments. From Beck and Arnold's discussion, it appears that in order to compare the relative magnitudes of the sensitivity

functions, we should normalize the functions with both the nominal values q_n and the standard deviations of the measurements σ_j. Then, if the standard deviations happen to be equal for all measurements, we only need to normalize with the nominal parameters as suggested by Lehman and Stark.

Although Arnold and Beck's suggestions on normalizing the sensitivity functions appear to be clear, there is confusion in its applicability. It seems that Beck and Arnold were making their suggestions of normalizing the sensitivities for the case of the unweighted least squares error function. (BECK77: 346-349) No comment is made concerning the impact of estimating with the weighted least squares error function. Lehman and Stark do not specify at all what their error criterion is. It may be possible, however, that they too were announcing techniques that assumed an unweighted least squares criterion. At any rate, there are uncertainties in the author's mind as to how we might properly weight the sensitivity functions in order to directly compare their relative magnitudes. It is not well known by the author how the choice of the error function relates to the proper weights.

For the case of the Open Chamber Hexane Model, the standard deviations of the measurements are not known. Thus, we could not properly normalize the sensitivities by their standard

deviations even if we wanted to. In addition, since the weighted least squares error function was used, we are not sure how the sensitivity functions should be normalized in order to compare exactly the effects of the parameters on the error function. Thus, only the unweighted sensitivity functions were considered and plotted in this section. These uncertainties about weighting the sensitivity functions most likely can be resolved with some effort. The effort required, however, is beyond the scope of this thesis project. Still, the unweighted analysis can serve us as an introduction to the reader on how an experiment can be designed.

Some Sensitivity Functions of the Current Experiment on the Hexane Model. Before describing the sensitivity plots, we first recall that in the Hexane Model there were 7 unknown parameters. This fact implies that 7 sensitivity functions exist for every differential equation in the Hexane Model. But, since there are only three measurement models in the Hexane Model, only the sensitivity equations for these three measurements need examination. With three equations, the total number of sensitivity functions becomes 21. However, the 21 sensitivity equations represent one experimental run. Since there were 4 experimental runs each at different chamber concentration levels, then a total of 84 plots of the sensitivity functions is needed to study experimental influences on the

Model. To get an indication of how such a sensitivity analysis proceeds, 3 plots of the sensitivity functions are discussed. These 3 plots should be sufficient to introduce the basic concepts.

In Figure 6.1, three sensitivity functions involving VMAX3 and KM2I are plotted. The plots were chosen based upon the results of the post-experimental sensitivity analysis. It appeared that from the post-experimental sensitivity analysis the parameter VMAX3 had the most influence on the error function whereas the parameter KM2I had the least influence. A further examination of the sensitivity functions invloving the parameters VMAX3 and KM2I is likely to add insight into the results already obtained in the post-experimental sensitivity analysis. Thus, the choice was made to examine some sensitivities involving these two parameters.

Figure 6.1 presents sensitivity functions plotted for 2,5-hexanedione in body water for the first run of both VMAX3 and KM2I. We see that VMAX3 has a much larger magnitude than KM2I. This seems to support the results from the post-experimental sensitivity analysis that VMAX3 has a larger effect on the measurements than KM2I. Still, we cannot say for sure that the relative magnitudes in Figure 6.1 are directly comparable unless we had

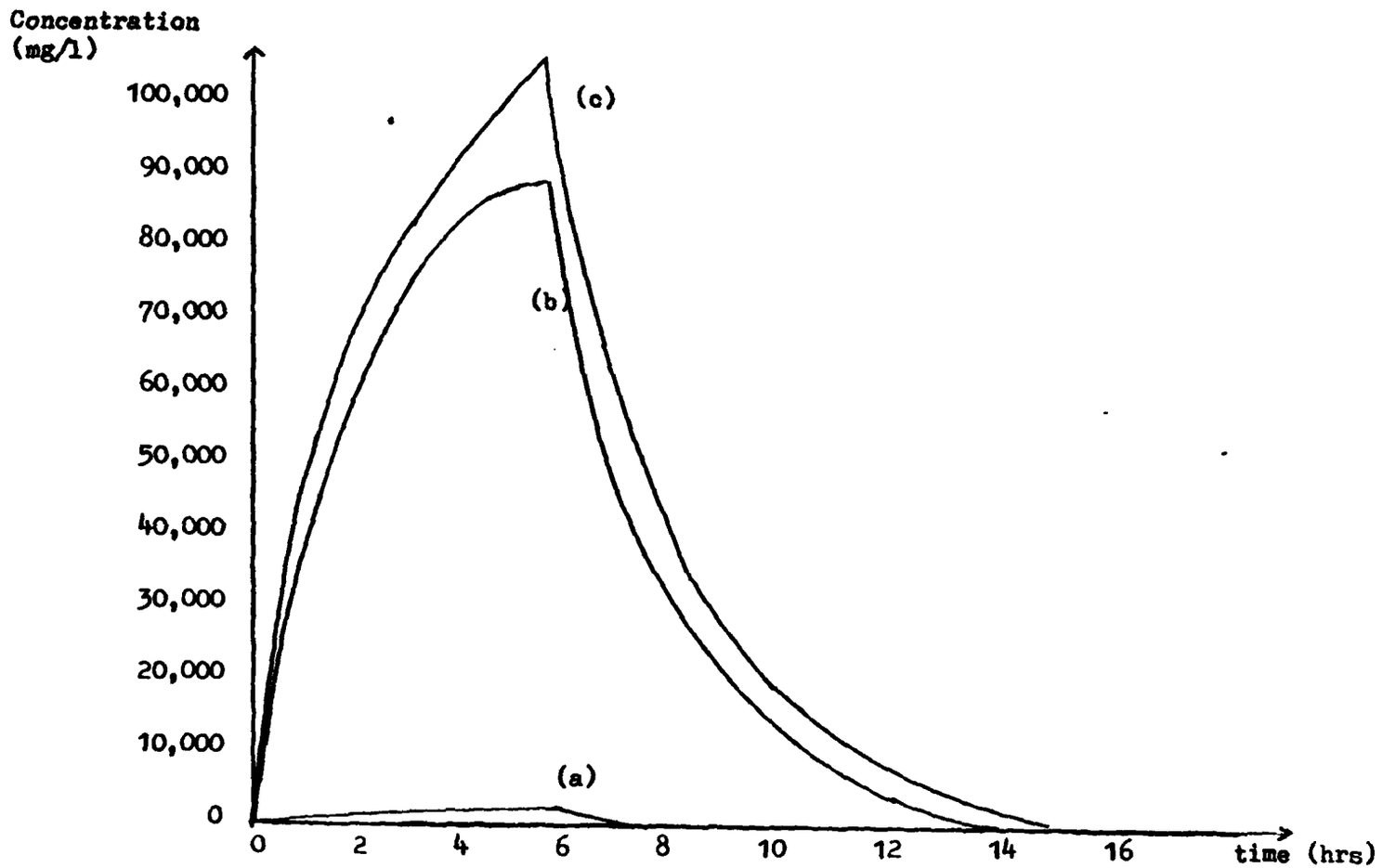

FIGURE 6.1 Sensitivity Function of 2,5-hexanedione in body water with respects to (a) KM2I: run #1 (b) VMAX3: run #1 (c) VMAX3: run #2

weighted them properly.

Another point of interest is that both VMAX3 and KM2I each give the largest sensitivity values at the time of 6 hours. This fact implies that the experimental observations collected from the concentration levels of 2,5-hexanedione in body water at the sixth hour should have the largest impact on measuring the parameters KM2I and VMAX3 precisely. Again, without the proper weightings, we are not sure how much will be the relative effects.

A second comparison is next made only for the parameter VMAX3, but at different concentration levels. The plot shows the sensitivities of 2,5-hexanedione for runs #1 and #2. The sensitivity for run #2 is larger in magnitude than that for run #1. These two curves represent the same sensitivity functions, although the concentration levels of the hexane in the test chamber is different. Hence, these two curves are comparable. These plots imply that VMAX3 affects the concentration level of 2,5-hexanedione in body water in run #2 more than the concentration level in run #1.

Example of Using Sensitivity Functions to Design an Experiment. The four general topics under experimental design of dynamical systems were stated by Goodwin and Payne and quoted in Chapter III. This section will briefly describe how one of these topics might be

employed on the Hexane Model. Specifically, the topic is input design. Attention was placed on examin
input to increase the precision of the estimates.

In this section, only one input chamber concentration level of hexane was used. Furthermore, only two sensitivity functions are considered. However, the procedure for examining the sensitivity plots in this case also apply to other input concentration levels and other sensitivity functions.

The chosen input concentration level of hexane in this section is shown in Figure 6.2. The input chosen is a binary signal that alternates between the two values 0 mg/l and 3.5 mg/l. The question we want to answer is how can we experiment in order to estimate the unknown parameters more precisely? The two parameters that we shall arbitrarily consider here are KM2 and KFO.

Figure 6.3 shows the sensitivity of methyl-n-butylketone in the body water with respect to KM2. The plot is basically periodic as might be expected from a periodic binary input function. The highest values are at times 1 hour, 4 hours, 7 hours, ... This indicates that our estimates of KM2 will probably be the most precise when the data is collected at those times.

The plot of the sensitivity of 2,5-hexanedione in body water with respect to KFO is shown in Figure 6.4. This plot shows that

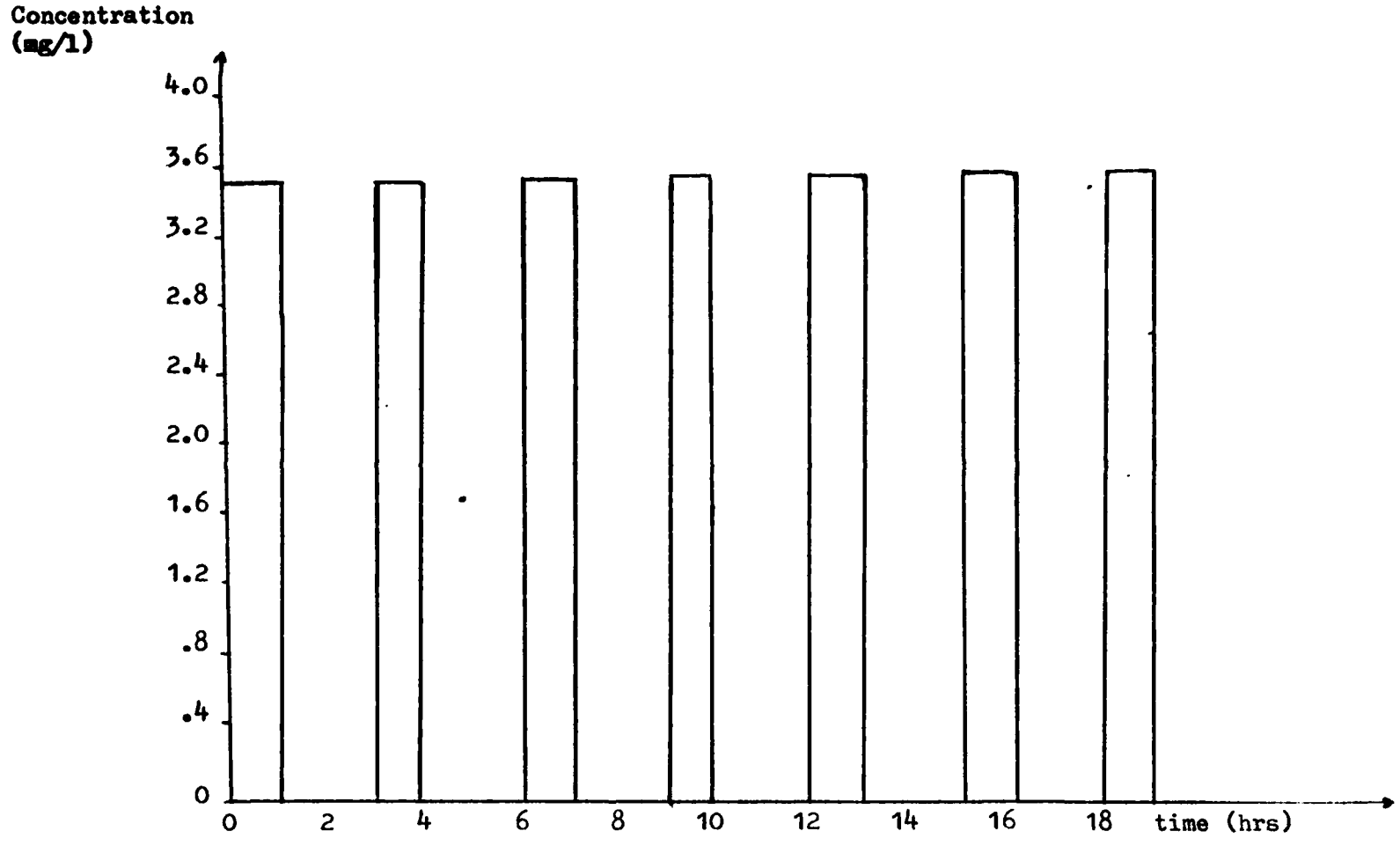

FIGURE 6.2 Input chamber concentration level

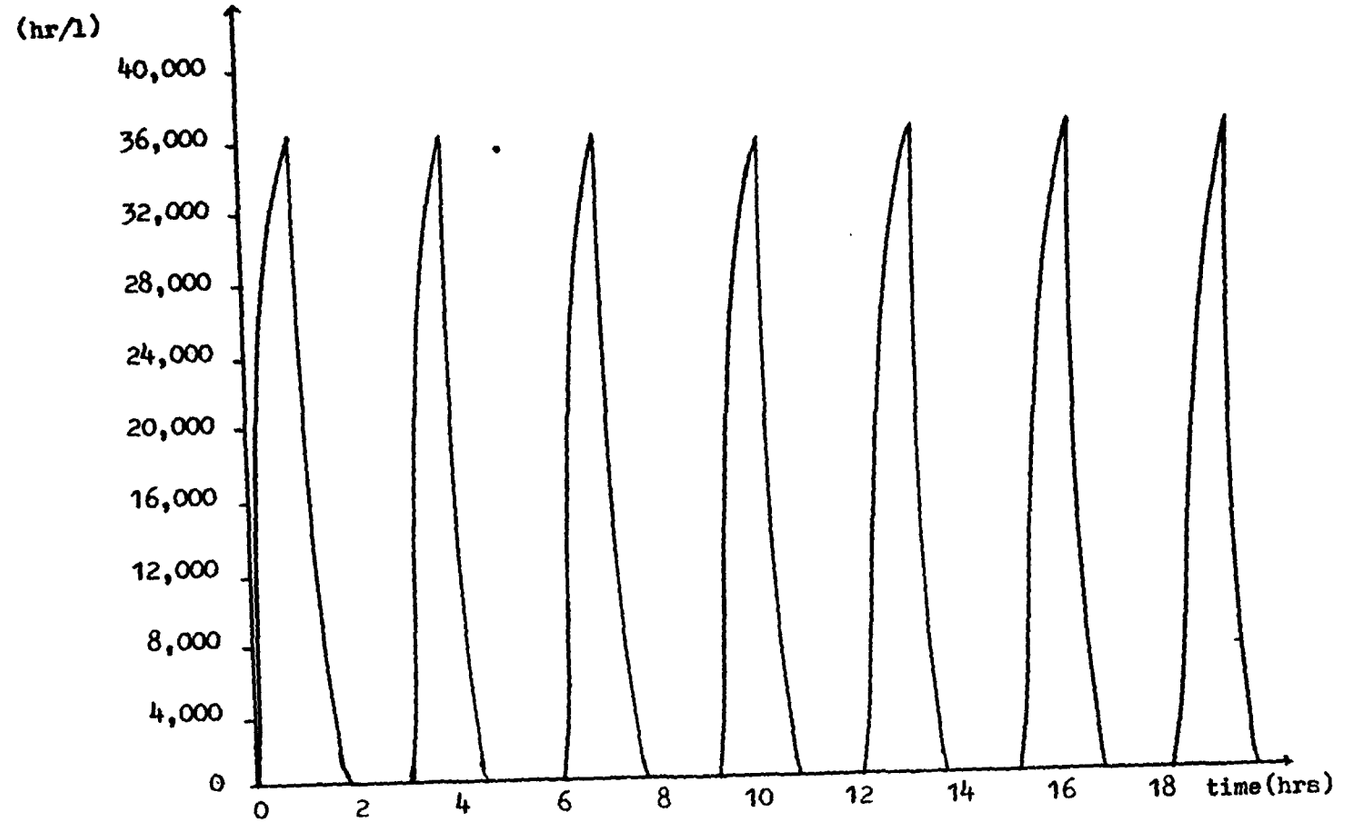

FIGURE 6.3 Sensitivity function of methyl-n-butylketone in body water with respect to KM2

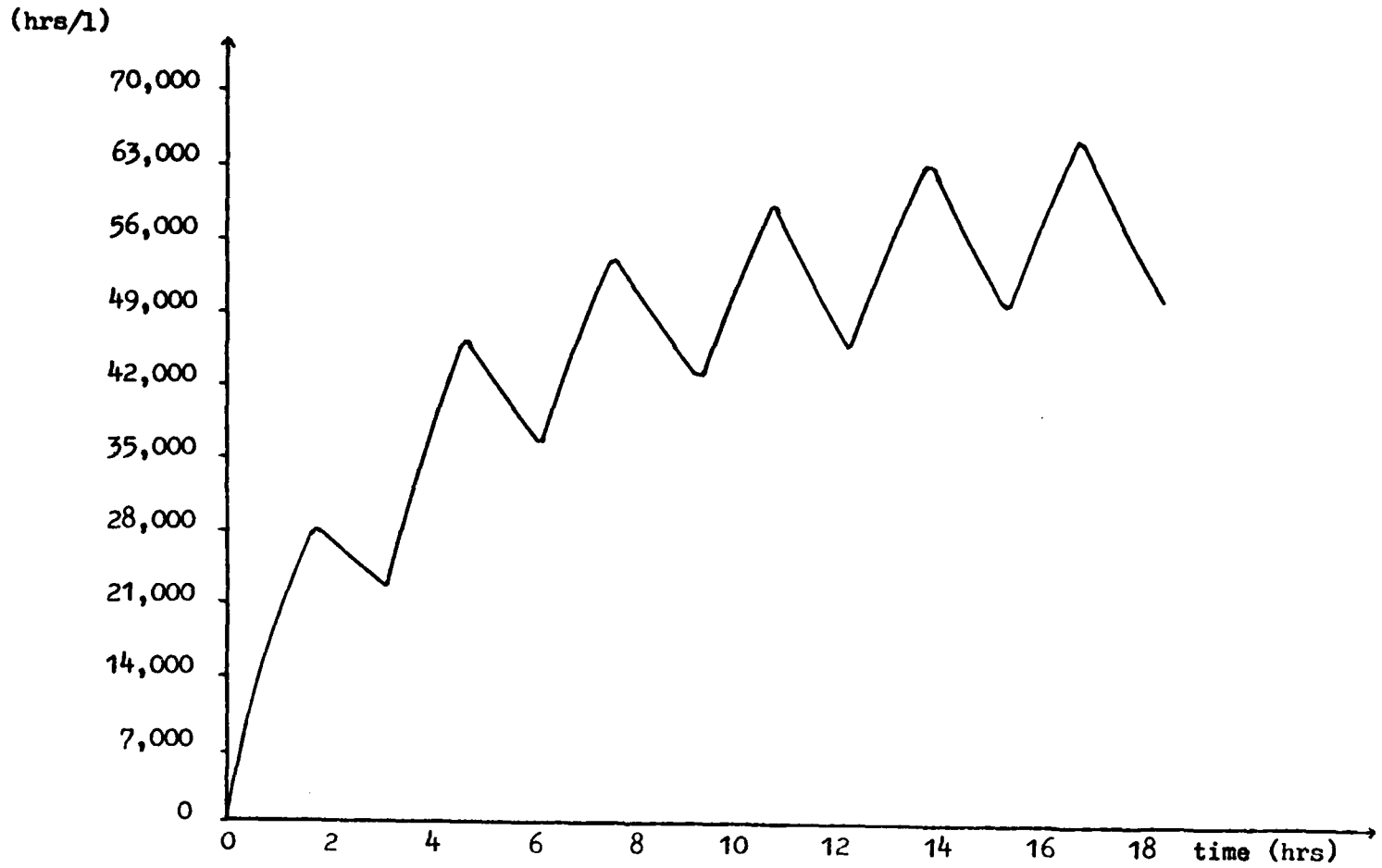

FIGURE 6.4 Sensitivity function of 2,5-hexanedione in body water with respect KFO

in order to get relatively high precision in estimating KFO, we should obtain experimental observations of 2,5-hexanedione in the body water at the points in time where the sensitivity is large. Some of the time points are 7.5 hours, 10.5 hours, 13.5 hours, and 16.5 hours. We might also sample at the points 1.5 hours and 4.5 hours, although these points do not have sensitivity values as large as the other points.

Now both plots involving the parameters KM2 and KFO are simultaneously compared to further determine how we should conduct the experiment. From the plots it appears that the most important experimental observation point for estimating KM2 is at the time of 1 hour. This is the point of the maximum difference between the sensitivities involving KM2 and KFO with KM2 on the high side. At this point we should expect that an experimental observation should affect the precision of KM2 with little influence from the effects of KFO.

By the same token, we note that at the local maximum points of the sensitivity function involving KFO, the sensitivity function involving KM2 approaches the value of zero. At the points 1.5 hours, 4.5 hours, 7.5 hours, and so on, the parameter KFO is likely to influence the experimental observations much more than the parameter KM2. Thus, by gathering data at these time points, we enable ourselves to more closely resolve the true value of KFO during

experimentation.

The brief examination we made of two sensitivity plots shows how one might be able to anticipate to some degree the precision of his estimates. This examination in fact can be applied to the many types of input concentration levels of interest. Then, from the examination, the researcher may be able to decide which input level best suits his objectives.

Sensitivity Functions for Designing Optimal Inputs. An extension of the previously stated methods of analyzing sensitivity functions is the procedure involving input optimization. In studying the plots of the sensitivity functions, an infinite number of inputs can be tried. However, using calculus of variations techniques, we can find input trajectories that afford the most precision possible with respect to a defined error function. Using this technique, we can avoid searching many input functions in order to select the one we desire for the experiment. (KALA82: 225-378)

VII. Conclusions and Recommendations

In sum, the major part of AFAMRL's problem was successfully solved. That is, the unknown parameters of the Open Chamber Hexane Model were assigned values that met approval of the researchers at AFAMRL. We note here that the primary factor in AFAMRL's acceptance of the final estimates in Chapter V was the information provided by the data plots. It is recommended that future parameter estimation algorithms include computer codes that plot the results when needed.

One interesting result is the success of the Scalar Gauss-Newton algorithm presented in Chapter IV. This algorithm is simpler to implement and faster to execute than the Gauss-Newton algorithm. In addition to these benefits, the Scalar Gauss-Newton algorithm also converges more in the sum of squares each iteration than the Gauss-Newton algorithm. As noted, however, is the fact that little effort was made to optimize the codes so that they would require the smallest amount of time possible to perform each iteration. It is recommend that these three algorithms in addition to any other algorithms still be considered in

future applications of pharmacokinetic models until they have been fully evaluated in terms of their performance.

Another point of interest brought out in this thesis is the use of sensitivity functions. In relation to the literature that exists, the discussion on sensitivity functions was brief. However, the discussion was extensive enough to indicate to AFAMRL how they may resolve some of their problems in designing experiments that afford more precision for their estimates. The author feels that further research and study is needed on this subject before a high degree of confidence can be achieved in using sensitivity functions. However, the power offered by sensitivity functions in designing experiments is sufficiently to warrant such a study.

To the author's knowledge, the only place where the equations of the Open Chamber Hexane Model are published is in this thesis. Originally, the equations were presented in a much different form. A great deal of effort was made towards putting the model equations into the form of a system of first order differential equations. It is recommended that the researchers put future model equations into the from of differential equations. This will help to avoid the errors that occur when someone else tries to formulate the equations in order to implement them on the computer. In addition, much time will be saved if the equations given by AFAMRL

are in the form that can be implemented on the computer immediately.

Finally, the author gained most of his conficence in the final estimates after examining many values closely surrounding the estimates. It is recommended that AFAMRL devote some time towards exploring the values around the estimates that they obtain. The estimates are not guaranteed to be global, and some type of scheme should be employed to indicate how close the estimates might be to the global. Only after examining the many values for the estimates can we be sure that our estimates are good.

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Methods for enhancing the parameter estimation process of pharmacokinetic models were examined and implemented for AFAMRL. The Open Chamber Hexane Model was the primary focus. Optimization algorithms were developed and used to estimate the unknown parameters in order that the model match closely with the experimental data. A sensitivity analysis was then conducted in two parts. First, the sensitivity of the estimated parameters to the error criterion was examined. Second, the use of sensitivity functions in designing future experiments was demonstrated. Finally, recommendations were provided for AFAMRL concerning future attempts in parameter estimation.


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